POLICY UPDATE

OCTOBER 2016

This is the second in a series of brief updates focusing on current policy issues related to antimicrobial stewardship and antibiotic resistance. Our first update highlighted current regulatory and voluntary initiatives aimed at enhancing antibiotic stewardship in US hospitals and long-term care facilities. This update summarizes recent policy initiatives in the United States aimed at reducing unnecessary or inappropriate outpatient antibiotic use, a key modifiable element in the rise of antimicrobial resistance. As always, we welcome feedback and discussion, including your suggestions for topics to explore in future policy updates. If you have comments or questions, please e-mail the CIDRAP ASP staff at asp-cid@umn.edu.

Outpatient Antimicrobial Stewardship

Antimicrobial use, overuse, and misuse all contribute to the proliferation of resistant organisms and reduce the lifespan of currently available antimicrobial agents (Marston 2016; CDC 2013a; Holmes 2016; Hicks 2011). The practice of stewardship involves commitments and strategies to optimize appropriate antimicrobial use, minimize unnecessary or inappropriate antimicrobial use, and improve overall quality of care. Since most healthcare-related antimicrobial use in the United States occurs outside of acute-care hospitals, critical access points for antimicrobial stewardship efforts are outpatient settings, including primary care and dental offices. Outpatient antimicrobial stewardship may require a different approach from hospital-based stewardship programs, but it also provides a key opportunity to substantially reduce the spread of antimicrobial resistance (Huttner 2011; Bell 2014; Wong 2016).

An estimated 12.6% of outpatient visits in the United States result in antibiotic prescribing (Suda 2013), leading to more than 250 million antibiotic prescriptions annually (Hicks, Bartoces et al. 2015; CDC 2013b). Most outpatient antibiotics are prescribed to treat common conditions such as bronchitis, influenza, and the common cold, which typically do not involve a bacterial infection and thus are not likely to improve with antibiotic therapy. In addition, overuse of broad-spectrum agents (eg, second- or third-generation cephalosporins or fluoroquinolones) in situations where more targeted antibiotics are sufficient is a concern in both pediatrics and adult healthcare (Spellberg et al. 2016; Jones 2015). For individual patients, antibiotic treatment can lead to potentially severe adverse effects, ranging from allergic reactions to community-acquired *Clostridium difficile* infections (Dantes 2015).

Defining 'Appropriate' Antibiotic Use

Distinguishing appropriate from inappropriate antibiotic use in a given situation may vary, depending on issues such as availability of alternative treatment options, individual susceptibility, and local resistance patterns (Spivak 2016; Spellberg 2016). Appropriate use is not necessarily defined by treatment guidelines (which may not reflect antimicrobial stewardship principles) or FDA-approved labeling, as noted by Spellberg and colleagues:

> *"For drugs other than antibiotics, appropriate use generally mirrors the way the drug was proven to be effective and safe in clinical trials. In contrast, effective and safe are necessary but not sufficient to define appropriate use of an antibiotic. For example, consider an antibiotic that has a broad spectrum of activity that includes both highly resistant bacteria and also more common susceptible bacteria for which many other antibiotics already exist. Use of such a drug*

to treat common susceptible bacteria drives resistance to the drug among bacteria that are more difficult to treat and for which no other options are available. Thus, even if the new antibiotic is safe and effective against susceptible bacteria, if it can also be used to treat more-resistant bacteria, its use to treat infections caused by susceptible bacteria would seem inappropriate as a first-line option (but may be appropriate in specific circumstances such as intolerance to or practical inability to use narrower-spectrum agents)." (Spellberg et al. 2016)

Recent efforts to develop best practices or treatment guidelines that are explicitly aligned with antimicrobial stewardship principles may help to define appropriate use of antibiotics for specific conditions. Key examples include antibiotic stewardship-concordant guidelines for treating acute respiratory tract infections in pediatric and adult patients (see below).

Baseline Data

CDC researchers and colleagues recently published an analysis of 2010 to 2011 data on antibiotic use in outpatient settings across the United States, focusing on total and appropriate antibiotic prescribing for all conditions (Fleming-Dutra, Hersh et al. 2016). The results provide a baseline rate of outpatient, oral antibiotic prescriptions by age and diagnosis and an estimate of the overall rate of total and appropriate antibiotic prescribing for adults and children. Diagnoses associated with the highest rates of antibiotic prescribing were sinusitis, suppurative otitis media, and pharyngitis. The authors noted that 50% of all antibiotic prescribing for acute respiratory tract conditions was considered appropriate; for all conditions treated in outpatient settings, 70% of antibiotic prescribing was considered appropriate. The resulting overall estimate of 30% *inappropriate* prescribing is cited as an indicator of outpatient antibiotic use that is potentially amenable to reduction through antibiotic stewardship (Tamma 2016; Marston 2016; Mehrotra 2016).

US Goal: Reduce 50% of All Inappropriate Outpatient Antibiotics

The US National Action Plan for Combating Antibiotic-Resistant Bacteria, released in March 2015, emphasized that changing the way antibiotics are prescribed is critical to slowing the development and spread of antibiotic-resistant infections. Goal #1 calls for improved antibiotic stewardship across all healthcare settings (by expanding existing programs, developing new ones, and monitoring progress and efficacy) and strengthening educational programs promoting antibiotic stewardship aimed at physicians and the public. The plan set as a national goal a 50% reduction in inappropriate antibiotic prescribing in outpatient settings by 2020. In collaboration with CDC officials and other public health and infectious disease experts, the Pew Antibiotic Resistance Project analyzed recent national data regarding antibiotic prescribing for conditions commonly treated by primary care and emergency room providers and devised recommendations for meeting the National Action Plan's goal.

Pew's May 2016 report, Antibiotic Use in Outpatient Settings, focused on treatment for acute respiratory tract infections, given that a large portion of antibiotic prescriptions for these conditions may be unnecessary. It distinguished conditions for which antibiotics are considered appropriate and necessary (such as nonviral pneumonia) from those for which antibiotic therapy is ineffective and unnecessary, such as common viral conditions like influenza. The Pew report identified specific targets for reduction in antibiotic prescribing by condition and age-group, listed in Table 1.

Table 1. Goals for Reduction in Outpatient Antibiotic Prescribing	
Condition Treated	**Reduction Target by Age-Group**
Sinus infections	9% (0-19 years); 51% (20-64 years); 16% (65 and older)
Pharyngitis	34% (0-19 years); 75% (20-64 years)
Middle ear infections (suppurative)	10% (0-19 years); 33% (20-64 years)
Middle ear infections (nonsuppurative)	100% (all age-groups)
Viral upper respiratory infections	100% (all age-groups)
Bronchitis/bronchiolitis	100% (all age-groups)
Asthma/allergy	100% (all age-groups)
Influenza	100% (all age-groups)
Viral pneumonia	100% (all age-groups)
Other conditions	25% (0-19 years); 19% (20-64 years); 10% (65 and older)
Source: Pew. Antibiotic Use in Outpatient Settings, May 2016.	

In theory, meeting these reduction targets would result in a 15% overall reduction in outpatient antibiotic prescribing, or approximately 23 million fewer courses of antibiotics prescribed per year. Based on the CDC's estimate that 30% of outpatient prescriptions (47 million annually) are inappropriate, this would correspond to approximately a 50% reduction in inappropriate antibiotic use in outpatient settings. In addition, a 10% decrease in outpatient antibiotic prescribing rates could result in a lower incidence of *C difficile* infections in the community (Dantes 2015).

Factors Driving Inappropriate Antibiotic Prescribing

Several recent studies have examined data on antibiotic use in outpatient settings to identify possible causes of inappropriate prescribing and to inform efforts to reduce it. Key variables include: providers' geographic region (highest prescribing rates in the southern United States), providers' medical specialty (highest rates among family medicine specialists), providers' individual patterns, and patients' health plans (Jones 2015; Fleming-Dutra, Hersh et al. 2016; Roberts et al. 2016; Barlam 2015).

The lack of available stewardship-concordant treatment guidelines or rapid diagnostic tests to identify antibiotic-susceptible infections also may contribute to inappropriate prescribing of antibiotics in outpatient care. Given that common viral illnesses (eg, common colds, sinusitis, and acute bronchitis) account for a large proportion of antibiotic use in these settings, factors other than specific medical need may be driving inappropriate prescribing. These include immediate psychosocial factors favoring inappropriate prescribing, which may outweigh potential factors deterring such prescribing, summarized in Table 2 below.

Table 2. Possible Factors Affecting Providers' Antibiotic Prescribing Patterns in Outpatient Settings	
Possible factors *driving* antibiotic prescribing	• Belief that patient/parent wants antibiotics • "Just to be safe" and avoid potential complications • Fear of being wrong • Reluctance to explain why antibiotics are unnecessary • Habit
Possible factors *deterring* antibiotic prescribing	• Risks of adverse effects and drug interactions • Motivation to support antibiotic stewardship • Preference for following antibiotic stewardship-concordant guidelines • Motivation to improve quality of care and decrease excess healthcare costs
Sources: Mehrota 2016; Spellberg 2016; Gerber 2016	

Stewardship Interventions

Various strategies implemented singly or in combination to support antibiotic stewardship in outpatient settings have been suggested, although no clear consensus on a set of best practices has emerged. Potential strategies include the following options, which have been described in the literature and in some cases evaluated (Table 3):

Table 3. Potential Outpatient Antibiotic Stewardship Interventions
Information-Based Strategies
• Active, personalized provider and patient education
• Introduction of antimicrobial stewardship-concordant treatment guidelines
• Diagnostic testing (eg, rapid antigen and C-reactive protein testing)
• Comprehensive education on antimicrobials and stewardship in medical school curricula
• Public awareness campaigns
Social and/or Behavioral Strategies for Providers
• Use of suggested alternatives messages on electronic health records stating that antibiotics are generally not indicated for a diagnosis and providing suggestions for non-antibiotic alternatives
• Accountable justification and/or order entry systems with explicit justification for antibiotic prescribing
• Peer-comparison messages
• On-site clinician educational sessions followed by personalized, quarterly audit and prescription feedback
• Routine audits to enhance accountability regarding prescribing rates compared with peers or available practice guidelines
• Public disclosure of data on antibiotic prescribing patterns
• Communication skills training (eg, regarding assumptions about patient expectations for antibiotics or about positive treatment options, such as non-antibiotic recommendations for symptom relief)
• Clinical decision support tools (eg, clinical guidelines, flowcharts, electronic alerts) integrated with electronic health records
• Financial incentives
• Interdisciplinary collaboration between specialists
Strategies for Patients/Parents
• Self-triage tools to help patients avoid office visits for common, self-limiting illnesses
• Back-up or delayed prescribing (“watchful waiting”)
• Time limits on prescriptions
• Posters displayed in providers’ examination rooms expressing commitment to appropriate antibiotic use
Sources: Dar 2016; Demijrian 2015; Dik 2016; Drekonja 2015; Fleming-Dutra, Mangione-Smith et al. 2016; Gerber 2016; Gerber 2013; Gravatt 2016; Jones 2015; Jørgensen 2016; Mauffrey 2016; Meeker 2016; Meeker 2014; PEW 2016; Roberts 2016

Policy Initiatives

To meet the goals outlined in the 2015 National Action Plan for Combating Antibiotic-Resistant Bacteria, the US federal budget for FY 2016 allocated $1 billion, an increase of more than $400 million from the previous year, to address the threat of antimicrobial resistance. The FY 2016 budget included $835 million to the Department of Health and Human Services (HHS). The president’s budget request for FY 2017 includes an additional $94 million (for a total of $1.1 billion) to continue these efforts (Cabezas 2016; PACCARB Second Public Meeting 2016).

The need to enhance antibiotic stewardship in outpatient settings is addressed in various ways in the National Action Plan. Key HHS activities aimed at outpatient antimicrobial stewardship, along with collaborative activities led by professional organizations, are summarized below.

Centers for Disease Control and Prevention (CDC)

The CDC's FY 2017 budget request includes an increase of $40 million above the FY 2016 level for the second year of its Antibiotic Resistance Solutions Initiative (CDC) to implement the National Action Plan. Antibiotic stewardship is one of the seven major components of the initiative. Goals of the stewardship component are listed in Table 4.

Table 4. CDC Antibiotic Resistance Solutions Initiative: Stewardship Goals
• Set national goals to improve antibiotic use (eg, reduce inappropriate prescribing by 50% in outpatient settings).
• Implement effective stewardship programs using the CDC's Core Elements guidelines regarding doctors' offices, hospitals, and nursing homes, integrated with sepsis early-recognition programs.
• Support collaboration to develop and evaluate stewardship activities.
• Provide data on antibiotic use and trends to better understand prescribing practices (eg, prescribing patterns in doctors' offices and strategies for improvement).
• Expand healthcare-associated infection/antibiotic resistance prevention programs at the state level to help implement best practices for antibiotic prescribing.
• Support early recognition of sepsis; heighten public awareness of sepsis and its complications and improve antibiotic use.
Source: CDC. Antibiotic Solutions Initiative (factsheet)

In November 2016, the CDC plans to release a new guidance document identifying core elements for antibiotic stewardship in outpatient settings (Hicks and Srinivasan 2016). The CDC will also host its annual Get Smart About Antibiotics Week campaign Nov 14-20, 2016, in collaboration with domestic and international partners, to coincide with the World Health Organization's World Antibiotic Awareness Week, the European Antibiotic Awareness Day, and related activities in other countries. The CDC's program is aimed at engaging stakeholders in a One Health approach to antibiotic stewardship in outpatient, inpatient, and animal health settings and to educate providers and the public about the consequences of inappropriate antibiotic use at the patient level and at the societal level (Hicks and Blaser 2015).

Through its ongoing educational program Get Smart: Know When Antibiotics Work, the CDC promotes appropriate use of antibiotics by providing practical information to support outpatient antimicrobial stewardship (Demirjian 2015), such as adult and pediatric treatment recommendations. The CDC consolidates recommendations from clinical practice guidelines into quick-reference tables to help guide optimal antibiotic use for common conditions treated in outpatient settings. The tables also include recommendations for over-the-counter medication for symptom relief when antibiotic therapy is not necessary or appropriate. Treatment recommendations from the CDC summarize the most recent professional guidance for treating patients with the following conditions in outpatient settings:

- *Adults*: acute rhinosinusitis, acute uncomplicated bronchitis, common cold or non-specific upper respiratory tract infection, pharyngitis, and acute uncomplicated cystitis
- *Children*: acute rhinosinusitis, acute otitis media, pharyngitis, common cold or non-specific upper respiratory tract infection, bronchiolitis, and urinary tract infections

In July 2016, the CDC's Healthcare Infection Control Practices Advisory Committee (HICPAC) published its Antibiotic Stewardship Statement for Antibiotic Guidelines, which provide recommendations to help professional organizations incorporate stewardship principles into guidelines for testing and treating infectious diseases. HICPAC recommended that organizations' guidelines include: (1) a hierarchy of antibiotic treatment recommendations with "first choice" antibiotics that optimize effective treatment

and minimize adverse effects, including the development of antibiotic resistance; (2) identification of advantages and disadvantages of antibiotic treatment choices regarding efficacy and adverse effects, including antibiotic resistance; (3) appropriate prescribing principles, such as providing the minimum effective duration of antibiotic therapy and using appropriate antibiotics with the narrowest therapeutic range and least risk of causing adverse effects.

Lauri Hicks, DO, director of the Office of Antibiotic Stewardship and Medical Director of the Get Smart: Know When Antibiotics Work program, and other CDC officials have collaborated with professional organizations to develop and publish clinical guidelines for appropriate antibiotic prescribing in outpatient settings. The following detailed antibiotic stewardship-concordant recommendations have recently been published:

- Adult patients with acute respiratory tract infections (Harris 2016), including a summary for patients
- Pediatric patients with upper respiratory tract infections (Hersh 2013)
- Dental patients (Fluent 2016)

Agency for Healthcare Research and Quality

HHS's Agency for Healthcare Research and Quality (AHRQ) supports research on antibiotic stewardship in various healthcare settings, including outpatient care, to strengthen the evidence base and develop improved methods for conducting and promoting antibiotic stewardship. AHRQ recently published two Evidence-based Practice Center reports relevant to outpatient antibiotic stewardship:

- *Early Diagnosis, Prevention, and Treatment of Clostridium difficile: Update* highlights significant improvements in diagnostics and updated recommendations for treating *C difficile* infection
- *Improving Antibiotic Prescribing for Uncomplicated Acute Respiratory Tract Infections* highlights interventions that have been shown to improve or reduce antibiotic prescribing in acute respiratory tract infections and not cause adverse consequences

Current priorities for AHRQ-funded research include the following initiatives:

- Development of antibiotic-resistance prevention tools that can be implemented by healthcare providers in long-term care, ambulatory, and hospital settings (as directed by the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria [PACCARB]), building on previous AHRQ-funded research on ways to reduce inappropriate antibiotic prescribing through stewardship programs.
- Funding pilot projects designed to develop and implement antimicrobial stewardship in ambulatory settings, as recommended by the 2012 SHEA/IDSA/PIDS policy statement on antimicrobial stewardship. AHRQ plans to award a research contract to support implementation of antibiotic stewardship in about 250 acute care hospitals, 250 long-term care facilities, and 250 ambulatory care settings (eg, physicians' offices, clinics, urgent care centers) nationwide, using AHRQ's Comprehensive Unit-based Safety Program model and CDC's Core Elements guidance in applicable settings.

Antibiotic Resistance Diagnostic Challenge

In the foreword to the final report of the Review on Antimicrobial Resistance (2016), Lord Jim O'Neill wrote that he found it "incredible that doctors must still prescribe antibiotics based only on their immediate assessment of a patient's symptoms, just like they used to when antibiotics first entered common use in the 1950s," without the benefit of diagnostic tests to identify and characterize bacteria. One of the Review's key outcomes was a recommendation to promote new, rapid diagnostics to reduce unnecessary use of antimicrobials, in part by encouraging the uptake and use of diagnostics in primary

and secondary care and by funding early research to develop new technologies for susceptibility testing and point-of-care diagnostics. In their recent review, Marston and colleagues (2016) also highlighted the critical need for rapid, simple point-of-care diagnostics in outpatient settings to help avoid empirical therapy and the unnecessary use of broad-spectrum antibiotics. Discussion at a 2015 workshop convened by the Wellcome Trust identified four operational strategies for using improved diagnostic tools to help guide clinical decision-making and enhance antimicrobial stewardship:

- Avoid unnecessary antibiotic use (to rule out bacterial infection, providing support for not treating)
- Optimize patient treatment and antibiotic use (to identify specific pathogens, characterize antibiotic susceptibilities, and guide targeted antibiotic escalation or de-escalation)
- Identify high-risk patients (to identify host biomarkers indicative of infection or prognostic for poor or positive outcomes of treatment)
- Improve drug development (to enhance appropriate patient recruitment into clinical trials)

A key goal in the 2015 National Action Plan is to enable the development and use of rapid and innovative diagnostic tests to identify and characterize resistant bacteria. One of the goal's supporting tasks is for HHS agencies to establish a prize for developing rapid diagnostic tests to improve treatment of drug-resistant infections and facilitate antibiotic stewardship. The PACCARB recommended two different awards, one of which would focus on a rapid simple test for use in outpatient settings (eg, for common upper respiratory infections and acute otitis media) (PACCARB 2016).

In September 2016, the National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA) announced the Antimicrobial Resistance Diagnostic Challenge, a federal prize competition calling for innovative ideas for rapid, point-of-care laboratory diagnostic tests to enhance antimicrobial stewardship specifically for outpatient as well as inpatient healthcare settings. The competition will award $20 million in prizes for new, accurate, and cost-effective in vitro diagnostic tests that would rapidly inform treatment decisions and thereby combat the development of antibiotic-resistant bacteria.

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