Chapter 1

The Need for Antibiotic Stewardship Programs
An Introduction

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Access to effective antibiotic therapy is essential to modern medicine. Not only are antibiotics lifesaving for the treatment of many infections, but they also provide the means for preventing and treating life-threatening complications among the growing numbers of patients receiving chemotherapy and stem cell and solid organ transplantation, thus making those therapeutic advances possible. However, antibiotic resistance has developed with each new drug introduced to the market. Although we know the development of resistance is almost certain with exposure to any antibiotic, inappropriate and/or unnecessary antibiotic use is accelerating the process. Realizing antibiotic resistance threatens the achievements of modern medicine, infectious diseases (ID) physicians, pharmacists, and public health officials have warned of the consequences of inappropriate antibiotic use for decades and advocated for preservation of these lifesaving drugs. Halting unnecessary antibiotic use has undoubtedly become one of the leading public health concerns of our time.

An estimated 50% of antibiotic use is inappropriate and/or unnecessary.[1–3] These estimates span inpatient and outpatient settings, various types of providers, and various indications or diagnoses, highlighting the breadth of the problem. Rates of antibiotic resistance have risen dramatically over the last 30 years. In 2013, the Centers for Disease Control and Prevention (CDC) estimated that 2 million people are infected annually in the United States with antibiotic-resistant bacteria, with at least 23,000 resultant deaths.[4] Additionally, roughly 453,000 people contract *Clostridium difficile* infections (CDIs) annually in the United States with nearly 30,000 deaths attributable to this single bacterium. CDI is frequently directly related to antibiotic use.[5]

Antibiotic stewardship programs (ASPs) date back to the 1970s and encompass multidisciplinary efforts to optimize antibiotic use.[6–8] Evidence has shown that effective ASPs not only reduce inappropriate antibiotic use but also improve patient safety and clinical outcomes.[9] Thus, ASPs have expanded across various healthcare settings in an effort to optimize antibiotic use and minimize adverse events and emergence of antibiotic resistance. This chapter focuses mostly on antibiotic stewardship efforts in the United States, although a brief discussion of global strategies is also addressed.

Numerous societies and public health officials have advocated for the expansion of antibiotic stewardship efforts across healthcare. In response to antibiotic overuse, evidence supporting the role of ASPs, and the critical threat antibiotic resistance poses to public health, they have called for mandatory implementation of stewardship through legislative and regulatory mechanisms.[10] These efforts culminated with the release of President Obama's *National Strategy for Combating Antibiotic-Resistant Bacteria* in September 2014, which outlines a framework for implementation of stewardship across the healthcare continuum, improved surveillance of antibiotic use, and national goals for reductions in inappropriate prescribing.[11] These

national goals lend new urgency to efforts to implement antibiotic stewardship strategies across healthcare settings and to develop standardized measures for appropriate antibiotic use.

Our goal in this chapter is to highlight the issues surrounding misuse of antibiotics that underscore the importance and need for ASPs, review evidence supporting the role of ASPs in improving patient care and safety, discuss policy initiatives and the evolution of antibiotic stewardship efforts to date, and underline next steps in preserving the precious shared resource of antibiotics.

Rationale for Antibiotic Stewardship Programs

The Scope of the Problem

Hospitals

Antibiotics are among the most frequently prescribed medications. Systematic surveys of inpatients at Boston City Hospital as far back as the 1960s found nearly 30% of patients received antibiotics during their hospitalization, with almost 10% receiving more than one antibiotic.[12, 13] Similar rates of antibiotic use have been reported in a variety of inpatient settings including acute care hospitals based in the community and tertiary care settings,[12, 14] as well as long-term care facilities (LTCFs).[15] Using data from a national administrative database of billing records for patients from a large sample of US hospitals, investigators from the CDC estimated 56% of patients discharged from 323 hospitals in 2010 received an antibiotic during their hospitalization.[3] These rates of antibiotic use have been reported among various patient populations, with the highest prescribing rates often among pediatric and surgical services.[14, 15]

More recent estimates of inpatient antibiotic consumption in the United States come from single or multicenter point-prevalence surveys. Although limited by lack of nationally representative samples and varying sources of data (e.g., pharmacy purchasing data, pharmacy order data, or antibiotic administration data), estimates have repeatedly found that nearly half of hospitalized adults and children receive an antibiotic during their hospitalization.[1, 16] Recognizing limitations of using indirect measurements such as administrative data to delineate the epidemiology of inpatient antibiotic use, CDCs' Emerging Infections Program (EIP) conducted an antibiotic use point-prevalence survey in 183 acute care hospitals across multiple states in one day in 2011.[1] The EIP is a network of ten state health departments and local collaborators representative of the US population. It conducts surveillance and evaluates methods for prevention and control of emerging IDs. Investigators determined not only the prevalence of inpatient antibiotic use across EIP sites, but also the most commonly used drugs and indications. Magill and colleagues found 50% of 11,282 inpatients evaluated received an antibiotic at some point during their hospitalization.[1] The most commonly prescribed drugs included vancomycin (14%), ceftriaxone (11%), piperacillin/tazobactam (10%), and levofloxacin (9%), in total accounting for approximately 45% of all antibiotic therapy.[1] This survey is one of the largest evaluations of inpatient antibiotic use in the United States to date. It confirms previous estimates of inpatient antibiotic use and additionally highlights the common use of broad-spectrum agents even for community-onset infections. The National Healthcare Safety Network (NHSN) recently launched the Antimicrobial Use and Resistance (AUR) Module, facilitating electronic reporting of antibiotic use data that will allow for prospective antibiotic use surveillance and assist with local and national stewardship efforts.[17]

Numerous evaluations of inpatient antibiotic prescribing quality have been conducted to estimate rates of inappropriate and therefore, modifiable antibiotic use. From these evaluations, 25% to 50% of inpatient antibiotic use is deemed inappropriate and/or unnecessary.[1–3] Common reasons for unnecessary or inappropriate antibiotic use include treatment of noninfectious or nonbacterial syndromes, treatment of colonization or contamination, use of overly broad-spectrum antibiotic therapy, and longer than necessary durations of therapy.[18] Most published assessments come from single center evaluations and focus on empiric and definitive drug selection.[14, 19–25] More recent evaluations involve in-depth evaluations of antibiotic prescribing including diagnostic evaluation, drug dosing, and duration of therapy.[26–31] No standard definition of inappropriate antibiotic use exists or is applied across studies, limiting interpretation of results and application to other settings. Most studies rely on expert opinion based on chart review to define appropriate therapy.[22, 23, 26, 28, 30, 32, 33] While more detailed in scope, these evaluations are often labor intensive and difficult to reproduce. Recently, large-scale national and multi-national antibiotic prescribing surveys have been conducted with the use of audit tools developed based on national guidelines and consensus expert opinion.[34–36] These tools are designed for use across various healthcare settings and by professionals of varying clinical expertise. For example, the Australian National Antibiotic Prescribing Survey (NAPS) is conducted annually using a published audit tool. The 2014 results showed a 38% prevalence of antibiotic use among inpatients, with nearly a quarter (23%) considered inappropriate.[37] In the United States, CDC in collaboration with external experts developed audit tools aimed at assessing the appropriateness of inpatient antibiotic use. These tools served as a foundation for the 2011 EIP Antibiotic Use Point Prevalence Survey, which on review of 296 inpatient antibiotic courses found prescribing could be improved in 37% of cases (40% of 111 urinary tract infection [UTI] cases and 36% of 185 vancomycin courses).[3] Standard audit tools are facilitating larger scale qualitative evaluations of antibiotic prescribing. With expanded use of electronic medical records, electronic audits may be possible in the future, making broader evaluations of antibiotic prescribing quality and real-time alerting of patients' charts for ASP review feasible.

Outpatient Settings

While we are gaining a better understanding of the epidemiology of inpatient antibiotic prescribing, the prevalence and various factors affecting antibiotic prescribing patterns have been better characterized for outpatient settings. Data from nearly 50 years ago shows antibiotics are the most commonly prescribed medication in outpatient settings, accounting for 15% of all prescriptions.[38] In 2009, antibiotic expenditures in outpatient settings in the United States totaled $10.7 billion, accounting for over 60% of all antibiotic expenditures across all healthcare settings.[39] Data highlighting the large role outpatient settings play in overall antibiotic use stresses the importance of effective outpatient antibiotic stewardship efforts.

Outpatient antibiotic prescribing rates are highest for children and for adults over the age of 65 years; 50–60% of all antibiotic prescriptions written are for acute respiratory infections (ARIs), which are largely viral in etiology.[40–43] While prescriptions for ARIs in children are declining,[40] data from the Veterans Affairs population and others suggests antibiotic prescriptions for ARIs in adults have remained relatively stable; 69% of Veterans received antibiotics for ARI diagnoses in 2012 as compared to 68% in 2005.[43, 44] Additionally,

broad-spectrum agents such as macrolides and fluoroquinolones are commonly used when either an antibiotic is not indicated or a narrower spectrum drug would suffice.[41, 43]

Further characterizations of outpatient antibiotic prescribing patterns have highlighted geographic and provider factors associated with high prescribing rates, potential targets for outpatient stewardship efforts. Higher outpatient antibiotic prescription rates are seen in southern states with family practice physicians prescribing the largest proportion of antibiotic courses.[42, 45] Interestingly, counties with higher proportions of obese patients, children under the age of two years, females, and prescribers per capita have higher antibiotic prescribing rates.[45] Substantial variation in providers' prescribing practices exists, and understanding factors associated with high prescribing is paramount to reducing unnecessary antibiotic use.[43] Interviews of primary care providers indicate providers are knowledgeable about guideline recommendations; however, they often stray from guideline recommendations due to the fear the infection is bacterial, belief that broad-spectrum antibiotics are more likely to cure the infection, and concern for poor patient and parent satisfaction if an antibiotic is not prescribed.[46] Additionally, knowledge of definitions of broad and narrow-spectrum antibiotic agents is poor;[46] therefore, providers may not understand the implications of the antibiotic choice. This information highlights variations in knowledge and attitudes around antibiotic use that may explain variation in practice (see Chapter 3) and should be tackled in order to limit unnecessary antibiotic use.

The Rise of Antibiotic Resistance and Other Adverse Events

Antibiotic resistance has been regarded as a modern phenomenon; however, resistance predates human use of antibiotics and evolving evidence implicates environmental organisms as reservoirs of antibiotic resistance genes. Resistance genes have been detected in 30,000-year-old permafrost sediment and culturable microbiome from a cave isolated from human contact.[47, 48] When populations of bacteria are exposed to antibiotics, susceptible organisms are killed and subpopulations harboring resistance genes may survive resulting in a population of antibiotic-resistant bacteria capable of causing subsequent infection in the host, or spread to others.[49] Additionally, new resistance mutations can develop upon exposure to antibiotics. The more antibiotics are used, the faster these processes happen.

We have seen this repeatedly since the first antibiotics were introduced into clinical practice over 70 years ago. As new antibiotics are released for clinical use, resistance to most is detected within five to ten years.[50] Case-control studies confirm the relationship between antibiotic exposure and subsequent antibiotic-resistant infections. For example, strong associations have been noted with antecedent carbapenem exposure and carbapenem-resistant *Klebsiella pneumoniae* infections. Similarly, receipt of cephalosporins has been identified as a risk factor for subsequent extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* and *Klebsiella* species infections.[51, 52] In 2013, CDC released a report providing the first overview of antibiotic-resistant organisms and other infections directly related to antibiotic use such as *Clostridium difficile*, and their threat to human health.[4] Carbapenem-resistant *Enterobacteriaceae*, drug-resistant *Neisseria gonorrhoeae* and *C. difficile* are among the most urgent threats. While antibiotic resistance is on the rise, development of new antibiotics has slowed,[53] highlighting the urgent need to curb unnecessary antibiotic prescribing and begin an era of responsible antibiotic use.

Antibiotic use is the single most significant risk factor for CDI.[54] Individual drug risks may vary, but nearly every antibiotic carries a threat of CDI with risk accumulating with

increasing numbers of drugs, dose and duration.[55] The epidemiology of *C. difficile* changed in the early 2000s with emergence of the North American pulsed-field gel electrophoresis type 1 (NAP1) strain. The NAP1 strain is associated with higher rates of infection, more severe disease, increased risk of relapse, and increased mortality.[56, 57] Not only has *C. difficile* become the most common cause of healthcare-associated infections in US hospitals, but it is increasingly reported in community settings as well.[58] Based on active population surveillance through CDC's EIP network that encompasses both inpatient and outpatient locations, it is estimated that nearly 500,000 incident CDIs occur annually in the United States, with nearly 30,000 deaths.[5] Although possibly influenced by use of more sensitive testing methods, increasing rates of this largely preventable infection are alarming. CDI has arguably become one of the most difficult infections of our time; antibiotic stewardship is and will continue to be a key component of its prevention.

CDI is one of the most severe adverse side effects resulting from antibiotic use; however, adverse drug events (ADEs) such as allergic reactions, drug toxicities, organ dysfunction, and unintended drug interactions may occur. Data suggest ADEs related to antibiotic use are not uncommon. An estimated 142,505 annual visits are made to emergency departments in the United States for antibiotic-related ADEs.[59] Antibiotics are implicated in 20% of all emergency department visits for ADEs, with the majority related to allergic reactions (78.7%).[59] Antibiotics are the most common drugs implicated in emergency department visits for ADEs in children.[4] Additionally, antibiotic ADEs in inpatients are associated with longer lengths of stay and higher hospital costs.[60] Providers do not always seem to appreciate the harms associated with antibiotic use; perhaps greater awareness of the harms of antibiotic use will bring about more judicious prescribing.

In summary, despite growing awareness of the harms of indiscriminate use, rates of antibiotic use have remained stable, and by some estimates have increased.[1, 43] Inappropriate and/or unnecessary antibiotic use is contributing to alarming rates of antibiotic-resistant infections and potentially life-threatening ADEs.

Evidence to Support Antibiotic Stewardship

Antibiotic stewardship is a multidisciplinary program of activities aimed at optimizing antibiotic use to achieve best clinical outcomes, while minimizing unintended adverse events and limiting selective pressures that drive the emergence of antibiotic-resistant organisms.[10, 61] Stewardship programs promote six principles of appropriate antibiotic use including prescribing: 1) for the right patients (e.g., only in patients with infections for which an antibiotic is indicated); 2) at the right time (e.g., as soon as possible in serious infections like sepsis); 3) with the right drug choice; 4) right route; 5) right dose; and 6) right duration of therapy. Antibiotic stewardship interventions have been shown to decrease antibiotic use, lead to more appropriate antibiotic use, reduce healthcare costs and antibiotic resistance, and most importantly, improve patient outcomes and safety.[62–64]

Impact on Antibiotic Use and Costs

Inpatient stewardship programs have shown significant improvements in antibiotic use in the form of both overall reductions in antibiotic consumption as well as more appropriate therapy, typically defined as improvements in drug selection, adherence to guidelines, and optimization of durations of therapy.[64] As an example, restrictions requiring prior authorization from ID for dispensing of third-generation cephalosporins led to an 86%

decrease in use of target drugs over a ten-year period at a large academic medical center.[65] Similarly, a comprehensive ASP including prior authorization for use of certain antibiotics, a comprehensive educational program, creation of local guidelines, and biannual feedback to providers on prescribing practices led to an overall 35% reduction in antibiotic use.[66] Prospective audit and feedback to hospitalists about prescribing habits for broad-spectrum antibiotics led to higher rates of appropriate antibiotic prescriptions from 43% at baseline to 74% post-intervention.[67] Camins and colleagues conducted a prospective cluster randomized trial assigning medicine teams at a large urban teaching hospital to either prospective audit and feedback focused on use of vancomycin, levofloxacin and piperacillin/tazobactam, or to use of indication-based guidelines for antibiotic use without any feedback.[68] Assessing nearly 800 prescriptions for vancomycin, levofloxacin, and piperacillin/tazobactam, intervention teams were more likely to prescribe antibiotics appropriately, compared with teams that did not receive the intervention, whether for empiric (82% vs. 73%) or definitive therapy (82% vs. 43%).[68]

These improvements in antibiotic use are achieved with the added benefit of reduced hospital costs, without negative impacts on mortality, length of stay, or readmission rates.[64] Reported annual cost savings from ASPs range from $150,000 to $900,000, with varying savings based on facility type and number of stewardship strategies implemented.[69–74] Conversely, Standiford et al. reported that discontinuation of an ASP at their hospital resulted in a 32% increase in antibiotic costs within two years of program discontinuation.[75] Antibiotic-related cost savings often plateau after initial reductions; however, this report underscores the ongoing role ASPs play in controlling antibiotic use and costs.

Antibiotic stewardship interventions aimed at improving outpatient antibiotic prescribing have been shown to reduce antibiotic prescriptions for conditions in which antibiotics are not indicated (e.g., ARIs) and improve choice when antibiotics are indicated.[76–78] Passive educational strategies such as use of printed educational materials alone have little to no impact as compared to active educational interventions including interactive meetings (vs. didactic lectures), individual provider level feedback and in-person education.[76, 77] Although impacts have been modest, clinical decision support (CDS) and care pathways provided either in paper form or integrated into the electronic medical record at the time of prescribing have been shown to reduce antibiotic prescriptions for ARIs and lead to more guideline-concordant management.[79–81] Patient-focused interventions, such as delayed antibiotic prescribing in which a patient is asked to wait a few days before starting an antibiotic to determine if the antibiotic is needed, can lead to reductions in unnecessary antibiotic use without negative impacts on symptom resolution, clinical outcome, or patient satisfaction.[82–84] Posters placed in examination rooms with the clinician's picture, signature, and commitment to use antibiotics appropriately led to a 20% reduction in inappropriate prescribing for respiratory conditions.[85] While several interventions have been shown to improve outpatient antibiotic prescribing, more effort is needed to better understand how to maximize their effect, which combinations of interventions provide the most benefit with available resources and how best to scale up outpatient stewardship interventions in a sustainable manner.

Impact on Antibiotic Resistance

The impact of antibiotic stewardship interventions on antibiotic resistance is difficult to assess given available data is often in the form of antibiograms that aggregate susceptibility data for only initial isolates. This precludes an evaluation of antibiotic resistance that

developed over time in hospitalized patients. Additionally, antibiograms- in their traditional form- do not allow for evaluation of multidrug resistance. These limitations combined with the additional factors influencing the development and spread of antibiotic resistance, such as lapses in infection control practices, make measuring the impact of stewardship interventions on antibiotic resistance difficult and results to date have been mixed.[86–88] However, studies have shown associations between antibiotic stewardship interventions and reductions in individual- and population-level antibiotic resistance. In a randomized controlled trial evaluating use of a clinical pulmonary infection score as criteria for antibiotic decision-making, investigators found randomization of patients with low risk of infection to short course empiric therapy as compared to standard of care, not only led to reductions in antibiotic use, but also reduced rates of antibiotic resistance and superinfections among patients receiving short course therapy (15% vs. 35%).[89] Implementation of a requirement for prior authorization of selected broad-spectrum parenteral antibiotics at one institution led to a 32% reduction in antibiotic expenditures coupled with increased activity against Gram-negative organisms for all targeted agents.[69] Interestingly, susceptibilities to both restricted and unrestricted antibiotic agents increased after the intervention, highlighting the selective pressure one class of antibiotics can exert on others.

Impact on CDI and Clinical Outcomes

Arguably one of the most important impacts of ASPs has been their contribution to reducing hospital rates of CDI. Antibiotics are the single most important risk factor for CDI; therefore, stewardship interventions promoting judicious antibiotic use are imperative for prevention. Guidelines recommend implementing an ASP as part of multidisciplinary efforts paired with infection control to prevent CDI in hospital settings.[90, 91] Multiple studies demonstrate the significant impact of ASPs on minimizing CDIs. A comprehensive antibiotic stewardship intervention at a community hospital involving antibiotic detailing with individual provider education as well as automatic stop orders resulted in a 22% decrease in broad-spectrum antibiotic use and a drop in CDI incidence from 2.2 to 1.4 per 1,000 patient days.[74] Decreasing rates of healthcare-associated infections (HAIs) due to resistant *Enterobacteriaceae* were also noted.[74] A combined strategy of restricted use of cephalosporins, a complete ban on fluoroquinolones and infection control measures resulted in termination of a toxigenic NAP1 CDI outbreak in the Netherlands in 2005.[92] After infection control measures were unable to control a hospital outbreak of NAP1 CDI in Quebec, implementation of a nonrestrictive stewardship intervention including dissemination of local guidelines combined with prospective audit and feedback resulted in reductions in antibiotic consumption followed by a marked 60% decrease in CDIs.[93] These studies highlight the significant impact ASPs can have on reducing CDIs. Nearly 30,000 people die annually from CDI in the United States;[5] minimizing unnecessary antibiotic use is critical to preventing this devastating infection and saving lives.

Optimizing antibiotic therapy improves patient outcomes including increased infection cure rates and possible reductions in mortality. Implementation of a guideline to promote effective prescribing for community-acquired pneumonia was associated with decreased 30-day mortality across a large health system.[94] Additionally, growing evidence suggests involvement of ID specialists in the management of patients with *Staphylococcus aureus* bacteremia leads to more appropriate and guideline-concordant management as well as reductions in hospital mortality.[95, 96]

Antibiotic stewardship is a patient safety initiative aimed at preventing antibiotic-associated harms. In addition to CDI, ASPs play an integral role in promoting patient safety through reductions in ADEs,[97] and by working with multidisciplinary teams to improve perioperative surgical prophylaxis in hopes of preventing surgical site infections. Hospitals with pharmacists performing therapeutic drug monitoring of vancomycin and aminoglycosides have lower rates of renal impairment, hearing loss, and overall mortality.[98] In many institutions, therapeutic drug monitoring is performed or supervised by an ASP pharmacist in addition to antibiotic medication reconciliation, evaluation of discharge antibiotics and monitoring drug-drug interactions to avoid adverse reactions. ASPs also play a role in determining the nature of antibiotic allergies, minimizing false labeling of drug allergies that promote use of broad-spectrum therapy, recommending appropriate alternative therapy when necessary and preventing use of drugs to which patient are allergic.[99, 100] Optimizing perioperative antibiotic prophylaxis is associated with reductions in surgical site infections; [101, 102] measures evaluating perioperative prophylaxis are incorporated into The Centers for Medicare and Medicaid Services (CMS) value-based purchasing program. Pharmacist-directed management of perioperative prophylaxis has been associated with improved survival and decreased costs and length of stay.[103] Finally, an evolving body of literature underscores further opportunity to avoid harm by involving ASPs in evaluation of patients for outpatient parenteral antibiotic therapy (OPAT).[104, 105] Use of OPAT is on the rise, adverse events related to antibiotics are frequent, and an estimated 15–30% of use is avoidable or unnecessary.[104–106] ASPs play a pivotal and effective role in not only minimizing unnecessary antibiotic use, but importantly, avoiding unnecessary harm and costs.

Making Antibiotic Stewardship a Reality

Evolution of Antibiotic Stewardship Goals

Despite numerous concerns about misuse of antibiotics and calls for improved prescribing,[7, 8] coordinated efforts to raise awareness, improve prescribing and impact policy did not take hold until the mid-1990s. In response to increased recognition of unnecessary antibiotic prescribing in outpatient settings, the US CDC launched the National Campaign for Appropriate Antibiotic Use in the Community in 1995, which was subsequently renamed Be Antibiotics Aware in 2017.[107] This program focuses on common illnesses that account for the majority of antibiotic prescriptions written in outpatient settings, and works with a wide range of partners to not only raise awareness about the threat of antibiotic-resistant infections and adverse effects of antibiotics, but also provide various clinical and informational resources for providers and patients to improve antibiotic use. The program has expanded to measure and characterize outpatient antibiotic prescribing,[42] evaluate interventions to improve prescribing,[108] and develop policies and guidelines to promote appropriate outpatient antibiotic prescribing.[109, 110] The program also includes Antibiotics Awareness Week, a yearly observance in November to raise awareness about antibiotic resistance and the importance of judicious antibiotic use.[107] During this week, CDC partners with a variety of organizations and over 40 countries to educate clinicians, the public, policymakers, hospital administrators, and the media about the critical issue of antibiotic resistance.

National ID professional societies worked for years to address the rising tide of antibiotic-resistant infections through development of prevention and treatment guidelines, promoting and funding research, and advocating for effective policies to address antibiotic resistance. Recognizing the implications of rising rates of antibiotic-resistant pathogens coupled with dramatic declines in development of new antibiotic agents, the Infectious Diseases Society of America (IDSA) originally published guidelines for improving antibiotic use in hospitals in 1988.[111] This was followed by a joint publication on the topic by IDSA and the Society for Healthcare Epidemiology of America (SHEA) in 1997.[112] These societies more specifically promoted the concept of antibiotic stewardship when they released new guidelines in 2007.[61] This document outlines ideal ASP team members and needed resources as well as core and supplemental strategies for ASPs to improve antibiotic use; yet, it lacked practical details of how to implement an ASP. The 2007 guidelines were followed by an IDSA policy paper titled Combating Antibiotic Resistance: Policy Recommendations to Save Lives that recommended requiring ASPs in all US healthcare facilities.[113] This document recommended new incentives and requirements be established for implementation and maintenance of ASPs across all health care settings as just one part of a multi-faceted approach to address antibiotic resistance.[113] IDSA recommended ASPs be required as a condition of participation in federal CMS programs.[113] A companion policy statement on antibiotic stewardship published the following year by SHEA, IDSA, and the Pediatric Infectious Diseases Society (PIDS) echoed these calls for mandatory implementation of ASPs across health care and additionally outlined minimum program requirements that should be enforced, process and outcome measures to be monitored, and deficiencies in national antibiotic surveillance and research that need to be addressed.[10] SHEA in partnership with other organizations promoting antibiotic stewardship published a guidance document outlining the knowledge and skills necessary for physicians, pharmacists or other healthcare providers to develop and lead an antibiotic stewardship program.[114] Finally, IDSA and SHEA released recommendations for implementation and measurement in antibiotic stewardship in 2016, specifically outlining best approaches and interventions to optimize antibiotic use.[115]

Initial experience with regulation mandating processes to improve antibiotic use in the United States comes from the state of California. California Senate Bill 739, signed into law in 2006, directed the California Department of Public Health to require general acute care hospitals to develop a process for evaluating the judicious use of antibiotics with results jointly monitored by representatives and committees involved in quality improvement.[116] While Senate Bill 739 did not explicitly state ASPs be established, nor outline or require methods for intervening to improve antibiotic use, a preliminary assessment of its impact identified 22% of California hospitals instituting ASPs.[117] While antibiotic stewardship initiatives expanded under this regulation, barriers persisted including staffing constraints and lack of funding. In September 2014, California Senate Bill 1311 [118] expanded previous regulations and required that hospitals adopt and implement an antibiotic stewardship policy adherent with guidelines established by the federal government and professional societies with leadership required by either a physician or pharmacist with training in antibiotic stewardship. California not only learned that legislation is effective in expanding antibiotic stewardship initiatives, but also that the language of such mandates is integral to developing appropriately constructed and funded programs.

Antibiotic resistance is a public health issue and in many ways addressing it falls within the scope of public health services. At a federal level, US CDC has been involved with

Table 1 Core Elements of Hospital Antibiotic Stewardship Programs

1)	**Leadership Commitment:** Dedicating necessary human, financial and information technology resources.
2)	**Accountability:** Appointing a single leader responsible for program outcomes. Experience with successful programs show that a physician leader is effective.
3)	**Drug Expertise:** Appointing a single pharmacist leader responsible for working to improve antibiotic use.
4)	**Action:** Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e., "antibiotic time out" after 48 hours).
5)	**Tracking:** Monitoring antibiotic prescribing and resistance patterns.
6)	**Reporting:** Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff.
7)	**Education:** Educating clinicians about resistance and optimal prescribing.

promoting antibiotic stewardship activities for nearly two decades and has worked to make improving antibiotic use a national priority. CDC has worked to not only provide education about antibiotic stewardship, but also tools and resources to implement effective programs.[107] CDC has worked to describe the human impact of antibiotic resistance in the United States as well as the extent and patterns of our antibiotic use and opportunities for improvement.[1, 3, 4] In 2014, CDC published a report calling for implementation of ASPs in all hospitals and soon after released a document outlining core elements of successful hospital-based ASPs (See Table 1).[3, 119] While acknowledging some flexibility is needed to tailor ASPs to local resources and culture, CDC emphasized success is dependent on leadership and defined multidisciplinary approaches. For the first time, the CDC provided a framework for components of a successful ASP in the Core Elements of Hospital Antibiotic Stewardship Programs [119] and has since outlined core elements of antibiotic stewardship in nursing homes and core elements of outpatient antibiotic stewardship."[120, 121]

In September 2014, President Obama signed Executive Order 13676: *Combating Antibiotic-Resistant Bacteria* which addresses the policy recommendations of the President's Council of Advisors on Science and Technology (PCAST) and identified priorities for combating antibiotic-resistant bacteria further detailed in the *National Strategy on Combating Antibiotic-Resistant Bacteria.*[122, 123] The Executive Order instructed CMS to review regulations and ensure acute care hospitals and LTCFs have ASPs that implement best practices by 2020.[122] Additionally, the national strategy called for reductions in inappropriate prescribing by 20% in inpatient settings and 50% in outpatient settings by 2020 as a key strategy in reducing antibiotic resistance. The subsequent *National Action Plan for Combating Antibiotic-resistant Bacteria* further outlined steps for implementing these goals and the national strategy over the next five years (www.cdc.gov/drugresistance/pdf/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf).[11] In response to these national efforts, the Joint Commission published a new standard for the implementation of ASPs for hospitals, critical access hospitals, and nursing centers for accreditation, which became effective in January 2017.[124]

Similar warnings about the threat of antibiotic resistance and calls for improved antibiotic use have echoed around the world. The World Health Organization (WHO) published a report on global antibiotic resistance in 2014, which describes not only global