Antibiotic Resistance and the Core Functions of Public Health

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ABSTRACT

Antibiotic resistance has become a major problem in public health. This resistance has been a growing issue due to years of inappropriate use of antibiotics. Hospitals are the most prevalent settings where bacterial infections occur related to antibiotic resistance. Some hospital infections cannot be treated because the bacteria are resistant to all currently available antibiotics. However, a program has evolved that helps to combat this.

Antibiotic stewardship fights the inappropriate use of antibiotics. The Antibiotic stewardship program (ASP) uses two main interventions: Prospective audit with intervention and feedback, and Formulary restriction and preauthorization. These are two ways to monitor prescribing by health care providers which saves antibiotic availability.

As antibiotic resistance is a public health issue, the core functions of the discipline are utilized: assessment, policy development, and assurance. Assessment analyzes the need for the program, and where they should be delivered; policy proposes, from the assessment, plans and processes; and assurance makes sure that what was proposed is what is delivered. The Centers for Disease Control and Prevention (CDC) has developed a number of website programs that analyze the antibiotic resistance problem in this nation. Other CDC websites introduce and explain how an ASP can fight the development of antibiotic resistance. National policies are also being proposed for this issue.

ASPs are needed in all hospitals. The problem of antibiotic resistance is not going away and actions must be taken. Public health is in a unique position to address this problem, and the core functions are a useful template for the ASP to follow.

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CHAPTER 1

INTRODUCTION and BACKGROUND

Antibiotic resistance is a critical health crisis, especially in medical settings, where analysis by the core functions of public health can develop policies and programs to confront the issue. The Institute of Medicine describes the core functions of public health as Assessment, Policy Development, and Assurance (Turnock, 2012). These three main tenets of the discipline are designed to identify current issues affecting public health, form policies to deal with these problems, and implement programs to address the issues, and analyze results of the program to determine the success of the intervention.

Currently, the Centers for Disease Control and Prevention (CDC) estimates that “over two million patients are infected with antibiotic resistant organisms, resulting in approximately 23,000 deaths annually” (Antibiotic Resistance Threats in the United State, 2013). However, from the time of the discovery of penicillin in 1928, bacteria steadily have become more resistant (Dellit, T. H., Owens R. C., McGowan J.E. Jr, Gerding, D.N., Weinstein, R.A., Burke, J.P., . . . Hooton TM, 2007). A myriad of antibiotics have been discovered since penicillin, each eventually becoming less capable of treating bacterial infections. This cycle continues as each new antibiotic becomes less and less effective. In some cases, infections are not able to be treated at all. With a paucity of antimicrobials being produced by pharmaceutical companies, and very few being approved by the Food and Drug Administration (FDA), the situation is even dire.

Antibiotic resistance is caused ultimately by the overuse of antimicrobials (Dellit et al., 2007). An estimated 20% to 50% of all hospitalized patients are inappropriately prescribed antibiotics (Carling, P., Fung P, Killion A., Terrin, N. & Barza, N., 2003; LaRocco, A.2003). With this overprescribing, bacteria become more resistant to antibiotics. The problem is there are only a few antibiotics available to treat infections (Core Elements of Hospital Antibiotic Stewardship Program, 2015). Not only that, with this increased antibiotic use, there are fewer antibiotics to treat the more difficult infections.

One result of excessive antimicrobial usage is a gastrointestinal disease called *Clostridium difficile* infection (CDI). This disease is caused by the bacteria *C. difficile* (Antibiotic Resistance Threats in the United States, 2013). CDI is a debilitating illness causing severe diarrhea and colitis (Antibiotic Resistance Threats in the United States, 2013). This disease produces high morbidity and mortality with 250,000 hospitalized cases in the U.S. annually with 14,000 deaths annually (Antibiotic Resistance Threats in the United States, 2013).

Antibiotics have been around for nearly a century. Cures of many diseases occurred as these “miracle drugs” eliminated the fear of many infections. Now, however, that has been challenged by bacteria developing resistance to antibiotics, some to the extent that the infection is untreatable. There is a public health need for the control of this problem. Antibiotic stewardship, a program to eliminate inappropriate use of antibiotics, can be utilized to combat antibiotic resistance. Physicians, other healthcare providers, and administration must realize the valuable contribution an antibiotics stewardship program can add to reduce antibiotic resistance in their hospital, and save patient lives. The purpose of this paper is to discuss assessment of the amount of antibiotic resistance in the hospital, development of policies to decrease the resistance by utilizing antibiotic stewardship, and the result of outcomes to insure the success of the antibiotic stewardship intervention.

Antibiotic Stewardship Program

The increase in morbidity and mortality from bacterial resistance to antibiotics is a growing public health crisis. With the rising rate of multidrug resistant organisms (MDRO), increased antibiotic use, and increased CDI and adverse events, the threats posed by antibiotic resistance are significant for hospitals, communities, and individuals. There is a reality that must be faced. With increased unnecessary use of antibiotics, the faster they lose their effectiveness (White House Forum on Antibiotic Stewardship Convenes Government and Private Sector Leaders Committed to Improving Antibiotic Prescribing, 2015). Add to this, the reality that fewer new antibiotics are being produced that any overuse or misuse of antibiotics brings the world closer to the point where the simplest of infections may not be treatable. However, the greatest concern is not the evolution of bacteria—it is the inaction of people.

An action that needs to be implemented in all medical facilities where antibiotics are prescribed is an antibiotic stewardship program (ASP). In this program, smart policies and effective partnerships are essential and guide effective use of antibiotics. With the aid of these partnerships, the goal of the ASP is "to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use including toxicity, the selection of pathogenic organisms (i.e.—*C. difficile*) and the emergence of resistance" (Dellit et al.2007). Guidance is needed by the ASP to reach these goals, and enhance patient outcomes.

An ASP must have commitment from leadership (CEO, medical officers) to procure human, financial, and information technology (IT) resources. Without this, they will ultimately fail. The program takes a team effort. An infectious disease physician is required for his or her expertise, and is accountable for the program's outcome. Another core team member includes a clinical pharmacist with infectious diseases training. This member's knowledge of antibiotics and medication therapy management is of great value. Other team members (not all are necessary, but highly recommended) include a clinical microbiologist, IT specialist, infection control preventionist, and a hospital epidemiologist (Dellit et al., 2007). This group is tasked with a difficult problem. Prescribing errors in the hospital are quite common. For example, antibiotics are commonly and incorrectly ordered for lung infections which are often due to a virus rather than bacteria. Another is the unnecessary treatment of urinary tract infections (UTI). One of every three UTIs are overprescribed for unnecessary antimicrobial treatment. These antibiotics become at risk for resistance and could be saved for more critical, life-threatening infections (MacDougal, C. & Polk, R.E, 2005). These examples show how the prescribing of unnecessary antibiotic can occur.

Overprescribing of antibiotics can put patients at risk for CDI; however, by reducing hospital antibiotic use by 5% can lead to a 26% reduction in CDI (Making Health Care Safer, 2015). Also, patients treated with powerful, broad-spectrum antibiotics are three times more likely to acquire another more resistant bacterial infection (Chan R., Hemeryck, L., O'Regan, M., Clancy L. & Feely, J.,1995). The more infections are treated with more powerful, and many times unnecessary, antibiotic therapy, the more patients become vulnerable to resistant bacteria.

Two Major Intervention Types by ASP

Antibiotic stewardship utilizes two major active interventions in the hospital to reduce inappropriate use of antimicrobials: prospective audit with intervention and feedback and formulary restriction and preauthorization.

Prospective Audit with Intervention and Feedback

First, there is the prospective audit with intervention and feedback. This intervention allows prescribing physicians access to the entire antibiotic formulary. However, if the infectious disease physician or clinical pharmacist from the ASP detects inappropriate antibiotic treatment using computer software, they can correct the treatment, and have the opportunity to interact with the prescriber (Dellit, et al., 2007). A hospital utilizing the prospective audit and feedback intervention for over a 7-year period showed a 22% decrease in intravenous antibiotic therapy, decreased CDI, and reduced hospital-acquired infections (HAI) caused by Enterobacteriacea (Carling et al., 2003). Another study by Solomon and colleagues (Solomon, D.H., Van Houton, L. & Glynn, R.J., 2001) displayed a 37% reduction in days of unnecessary treatment by levofloxacin and ceftazidime, including a decrease in the start of other antibiotics. A smaller hospital, without the resources for a full-scale ASP, showed a 69% compliance with the ASP guidelines set by the hospital. This down-sized program resulted in an annual savings of $177,000 for antimicrobial expenditure (Levin, P.D., Idress, S., & Sprung, C.L, 2012). Another study (Fraser, G.L., Stogdill, P., Dickens, J.D., Wennberget, D.E., Smith, R.P. & Prato,, S. 1997) in a hospital utilizing prospective audit with feedback and intervention was conducted to analyze the acceptance of suggestions from the ASP and acceptance of those suggestions. In this study, 85% of the suggestions from the ASP were implemented. Also, there were 1.6 fewer days of intravenous therapy with no impact on clinical outcomes compared to controls. There was also a saving of $400 per patient.

Formulary Restriction and Preauthorization

The second type of intervention is formulary restriction and preauthorization. This antibiotic stewardship strategy limits the use of certain antimicrobials without preauthorization from an infectious disease doctor or pharmacist on the stewardship committee. In most hospitals, there is a committee that evaluates antibiotics for inclusion on the hospital formulary. Therapeutic efficacy, toxicity, cost, and redundancy of agents are considered as criteria for inclusion as acceptable antimicrobials for use. This more restrictive intervention has proven to be more effective at reducing the use of antibiotics. A study by Philmon and colleagues (Philmon, C., Smith, T., Williamson, S., & Goodman, E. 2006) tested the cost effectiveness of an ASP. In the almost 3-year study, a cost savings of nearly 1.9 million dollars was found due to the stewardship program. Recommendations by ASPs were also shown to increase antimicrobial appropriateness, clinical cure, and economic outcomes due to Formulary Restriction and Preauthorization (Dellit et al., 2007). However, in many other studies, (Quale, J., Landman, D., Aurina, G., Atwood, E., DiTora, V., & Patel, K.,1996; White, A.C., Atmar, R.L., Wilson, J., Cate, T.R., Stager, C.E., & Greenberg, S.B.,1997), this stewardship strategy showed an initial benefit; however, as the use of the restricted antibiotic lessened, the use of a new, preferred antibiotics emerged with the concomitant increased resistance (White, A.C. et al.,.1997). This phenomenon is known as “squeezing the balloon” where the restricted antibiotic becomes less resistant, but the “replacement” antibiotic becomes resistant (Burke, 1998).

Supplemental Antibiotic Stewardship Strategies

In addition to the two main active strategies for antibiotic stewardship described above, there are several supplemental intervention strategies. While these interventions complement the main strategies, they are more passive and less effective as the sole intervention (Dellit et al., 2007).

- **Education** is an effective and essential intervention for an ASP. These activities are essential to an ASP and include conference presentations, hospital staff presentations, and email alerts. However, education alone without one of the active strategies is a marginally successful intervention (Dellit et al., 2007).
- **Guidelines and clinical pathways** for antibiotic stewardship create standards for antibiotic treatment. These standards use evidence-based practice to make antibiotic treatment decisions (Dellit et al., 2007). The use of the interventions can be effective

despite physician resistance (Dellit et al.). Incorporating local patterns of antibiotic resistance can improve antimicrobial use and patient outcomes (Dellit et al.).

- **Antimicrobial cycling and scheduled antimicrobial switching** is an ineffective, yet often employed secondary strategy of antibiotic stewardship. With the proper implementation of this intervention, certain antibiotics are removed from the antibiotic formulary and may not be used without preauthorization. Most studies show that as an antibiotic is removed, another must be used, with eventual bacterial resistant to the new antimicrobial (Burke, 1998). An antibiotic switch is unlikely to reduce resistance.
- **Combination therapy** is the prescribing of two or more antimicrobials to cover all possible bacteria causing an infection. This strategy can be used for a variety of reasons including empirical therapy, improved clinical outcomes, and the prevention of antibiotic resistance. Serious infections require complete coverage of all infection types. However, many times, therapy is redundant and unnecessary (Dellit, et al., 2007).. Although, combination therapy may be necessary for empiric treatment, routine use of combination therapy is not recommended as an antibiotic stewardship strategy.
- **Streamline or de-escalation of therapy** is the re-evaluation of antibiotic therapy when microbiological therapy and antibiotic susceptibilities are available. This intervention aids in the judicious use of antibiotics. Empiric therapy is needed to optimize treatment for many infections; however, it also promotes the selection of resistant pathogens. This can be combated when culture collected from tissue or body fluids, and/or antibiotic sensitivities are available. Treatment can often be streamlined or de-escalated, especially when broad-spectrum antibiotics are initially used (Kollef, M.H. & Kollef, K.E., 2005). Cultures and sensitivities are usually available 48 to 72 hours after they are collected. A

study by Briceland and colleagues (Briceland, L.L., Nightingale, C.H., Quintiliani, R., Cooper, B.W., & Smith, K.S.,1988) showed that reevaluating therapy during this time frame by a physician or another member of the ASP led to a 54% increase in recommendation to change therapy and resulted in an annual savings of over $107,000.

- **Dose optimization** individualizes antibiotic therapy to improve treatment. This optimization accounts for individual characteristics (i.e.—age, renal function, weight), infected organ (i.e.—urine, pneumonia, skin), and pharmacokinetic and pharmacodynamic characteristics of the drug (Dellit et al., 2007). All of these are taken into consideration when beginning therapy. This will optimize the accuracy of treatment by use of the proper antibiotic and correct dosage.
- **Conversion from parenteral to oral therapy** is the effective and timely shift of antibiotic treatment from intravenous to oral delivery of the drug. This modification can result in reduced length of hospital stay, health care costs, and complications that may occur from parenteral (intravenous) treatment. This switch can only occur if certain clinical criteria are met. Nevertheless, it has been shown in studies that this conversion can significantly reduce costs with no effect on health outcomes (Chan R.et al., 1995).
- **Computer surveillance and decision support** aids physician decisions by accessing the patient's electronic medical records (eMR). With access to the eMR, a computer physician order entry (CPOE) system has the potential to decrease medical costs and antibiotic prescribing (Dellit et al., 2007). Progress in this endeavor has been slow. However, of particular success has been developed by the Latter Day Saints Hospital in Salt Lake City (Burke, J.P., Classen, D.C., Pestotnik, S.L., Evans, R. S., & Steven, L.E.,1991). This CPOE system can recommend antibiotic regimens and courses of

therapy. It even reviews the patient's chart for allergies, drug-drug interactions, and recommends a dosage (Burke, J, 1991). A study by Wang and colleagues (Wang, H.Y., Lu, C.L., Wu, M.P., Huang, M.H., & Huang, Y.B., 2012) demonstrated that hospitals utilizing a CPOE had decreased errors in prescribing compared to hospitals without a decision-support system. Another study by Chassin and Galvin, with the Institute of Medicine National Roundtable on Health Care Quality examined ways to improve health care. One of the main improvements needed was the increased use and quality of CPOE (Chassin, M.R. & Galvin, R.W., 1998). Studies have shown that when information technology is utilized for treatment decisions, there is a decrease in allergies and adverse reactions, length of hospital stay, improper antibiotic prescribing, and antimicrobial cost (Evans, R.S., Pestotnik, S.L., Classen D.C., Clemmer, T.P., Weaver, L. K., Orme, J. F. Jr…. Burke, J.P., 1998).

- **The Microbiology Lab** is also essential to an ASP. The clinical lab plays a critical role in an ASP by providing patient-specific culture results and susceptibility data. Accurate, expedient results are vital so treatment can be confirmed as correct or altered to optimize individual antimicrobial therapy.

Bacterial resistance has been developing since antibiotic therapy began. This resistance has been sustained, even as more antimicrobials were added for treatment. This continued relatively unnoticed as drugs to treat infections were still reasonably available. However, now that new antibiotics are scarce, many infections have become more difficult and sometimes impossible to treat.

A program is needed to confront this disturbing trend. The judicious use of antibiotics in healthcare settings is critically needed. To coordinate such an effort, an ASP can be implemented for appropriate usage of antibiotics, and improved outcomes. As a public health issue, ASP can utilize the core public health functions to evaluate the program.

CHAPTER 2

ASSESSMENT, POLICY, AND ASSURANCE

Assessment

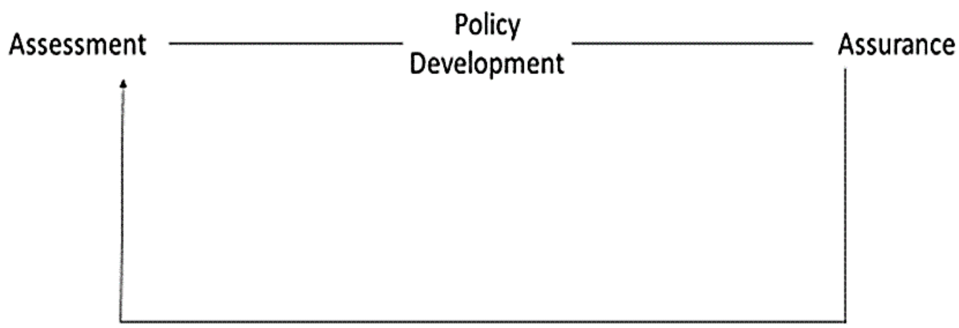
The core public health functions are to identify health problems (Assessment), implement policies to address the issues (Policy), and utilize strategies to assure the desired goals are achieved (Assurance). These core functions are displayed in Figure 2.1 (Turnock, 2012). Although a useful model, there is a limitation in that the model does not show the interactions between the separate functions (Turnock, 2012).

Assessment is a key to responding to and protecting the public's health and involves the identification of public health problems. This is an ongoing systematic collection and analysis of information used to assess the health of the community (i.e.—hospital patients). Health status and community needs are assessed utilizing epidemiologic data and other studies (Segigmas, 1981). An ASP in hospitals must assess the use of antibiotics and the outcomes. As a public health threat, the use of antimicrobials in one hospital affects patients in that hospital, other community hospitals, and the community in general because of increased antibiotic resistance. Improper antibiotic use causes bacteria to become resistant. These bacteria are spread from patient to patient in the hospital and in the community increasing resistance.

Local health systems strive to protect patients from antibiotic resistant bacteria by means of the ASP. While a coordinated approach is needed, a more independent effort is often utilized. In a preferred, idealized approach, acute care hospitals, long-term care facilities, and nursing homes would be connected to the public health department. This department would collect and analyze data and disseminate results to health care facilities and the community

Figure 2.1

Model of the Core Function of Public Health



Adapted from Rowitz, 2012

(Making Health Safer, 2015). This coordinated approach, headed by the local public health department, would provide a more comprehensive approach to community safety and protection from antibiotic resistance.

Assessment Measures

The measure of antibiotic use is essential to assessing the health threat that resistant bacteria pose to the hospital community. Increases in antibiotic use combined with the paucity of new antimicrobials being discovered or developed makes every prescription of these valuable resources very critical. Of concern are the scenarios where treating a simple infection, performing life-saving surgery, and the transplanting an organ will no longer be possible because the lack of available antibiotics. The risk is real. Antibiotics stewardship is needed to reverse this problematic trend.

Potential assessment criteria such as antibiotic usage in the hospital or resistant bacteria causing infection alert an ASP of problems concerning the amount of antibiotic prescribing and inappropriate use. Improper treatment of infections can be evaluated by measures including increased MDRO, increased morbidity, and increased mortality due to unnecessary antibiotic treatment (including CDI). One example, the inappropriate use of antibiotics to treat normal flora collected from urine cultures is not needed in this situation. Timing of prophylactic treatment for surgical procedures is another area in need of revising. Ideally, the antibiotic used for prophylaxis should be concentrated at the incision site and delivered properly, approximately 15 minutes before surgery (Dellit et al., 2007). If not executed correctly, bacterial resistance may occur in the patient (Dellit, et al., 2007). Proper use of antibiotics can greatly decrease unnecessary antibiotic treatment, thus keeping valuable antibiotics from becoming resistant.

In 2013, the CDC published an article outlining the 17 biggest threats to the public's health in the U.S. due to antibiotic resistance (Antibiotic Resistance Threats in the United States, 2013). Some of these threats have existed for decades or more and are still a major concern, while others are emerging problems. These 17 threats show how extensive the problem of antibiotic resistance is, and how essential antibiotic stewardship has become to the health of the public (See Table 2.1).

Of the bacteria on the CDC's antibiotic resistance list, there are a few bacteria that are a threat to public health but are not a direct threat in hospital patients and other medical care facilities. A summary of the more prevalent resistant bacteria found in health care settings and under the guidance of the ASP are listed below.

Urgent Healthcare Threats

C. difficile

- Causes life-threatening diarrhea
- Excess antibiotics destroy normal flora of the gastrointestinal tract
- 250,000 infections per year in the US requiring hospitalization
- 14,000 deaths annually
- Deaths have increased 400% from 2000 to 2007
- Almost half of all infections occur in people less than 65 years old, but 90% of deaths occur in people 65 years and older

Table 2.1

Antibiotic Resistant Bacterial Threats

Usually Cause Hospital-Related Infections	Usually Do Not Cause Hospital-Related Infections
C. difficile	**Drug-resistant *Neisseria gonorrhoeae***
Carbapenum-resistant Enterobacteriacea	**Drug-resistant non-Typhoidal Salmonella**
Multi-drug resistant *Acinetobacter*	**Drug-resistant *Salmonella typhii***
Extended-Spectrum β-lactamase (ESBL) producing Enterobacteriacea	**Drug-resistant *Shigella***
Vancomycin-resistant Enterococci (VRE)	**Drug-resistant *Campylobacter***
Multi-drug resistant *Pseudomonas aeruginosa*	
Drug-resistant *Streptococcus pneumonia*	
Drug-resistant tuberculosis	
Vancomycin-resistant *Staphylococcus aureus* (VRSA)	
Erythromycin-resistant Group A *Streptococcus*	
Clindamycin-resistant *Streptococcus*	
Multidrug-resistant *Acinetobacter*	

(Adapted from Antibiotic Resistance Threats in the United States, 2013)

Carbapenem-resistant Enterobacteriacea (CRE)

- Increases seen in patients in medical facilities
- Resistant to nearly all known antibiotics
- Resistant to carbapenem, the antibiotic of last resort
- 9,000 Healthcare Associated Infections are caused by CRE each year
- 600 deaths per year are caused by CRE

Multi-drug resistant *Acinetobacter*

- Causes pneumonia and bloodstream infections among critically ill patients
- Some strains resistant to most available antibiotics; 63% resistant to 3 classes of antibiotics
- 12,000 *Acinetobacter antitratus* infections occur in the US
- Almost 7,000 are multidrug resistant
- About 400 deaths annually are attributed to these infections

Extended Spectrum β-lactamase (ESBL) producing Enterobacteriacea (ESBL-EB)

- Nearly 20% of all infections due to Enterobacteriacea are caused by ESBL-EB
- Patients with bloodstream infections caused by ESBL-EB are 57% more likely to die than patients with non-EBBL-EB bloodstream infections
- 26,000 drug resistant Enterobacteriacea occur annually with 1,700 deaths

Vancomycin-resistant Enterococcus (VRE)

- Mostly seen in patients receiving treatment for bloodstream, surgical site, and urinary tract infections
- Resistant to vancomycin, an antibiotic of last resort
- About 20,000 (or 30%) of enterococcal infections acquired in the hospital are vancomycin resistant

- 1,300 deaths annually are attributable to VRE

Multidrug-resistant *Pseudomonas aeruginosa*

- Some strains are resistant to nearly all or all available antibiotics
- About 13% of severe hospital infections are caused by multiple-antibiotic resistant *P. aeruginosa*
- There are more than 6,700 infections yearly due to multidrug resistant *P. aeruginosa* causing 440 deaths

Methicillin-resistant *Staphylococcus aureus* (MRSA)

- Causes a variety of infections from skin and wound to pneumonia and bloodstream infections
- The CDC estimates that over 80,000 severe MRSA infections occur annually and more than 11,000 deaths
- An unknown number of less severe MRSA infections occur annually

Drug-resistant *Streptococcus pneumoniae*

- Developed resistance to most commonly, and now less frequently used antibiotics
- Approximately 30% of S. pneumoniae infections are annually to be fully resistant to at least one clinically relevant antimicrobial
- There are 19,000 excess hospitalization annually due to this bacteria and more than 7,000 deaths

Drug-resistant Tuberculosis (TB)

- Multi-drug resistant TB is showing resistance to INH and rifampin, essential first line antibiotics
- Extensively drug-resistant (XDR)-TB is showing resistance to first-line and second-line antibiotics (ie—amikacin, kanamycin and capreomycin)

- The CDC reported that there were 10,528 cases of TB in the U.S. in 2011 with 10% being MDR-TB (Antibiotic Resistance Threats in the United States, 2013).

When an ASP is implemented, there is a need for assessment of antibiotic resistance. Antibiotic resistance is at the point where the number of extensively resistant bacteria is increasing (Antibiotic Resistance Threats in the United States, 2013). After years of ignoring this problem, an antibiotic stewardship program is desperately needed in hospitals and other healthcare settings to alleviate the negative outcomes of overuse and misuse of antimicrobials.

Policy Development

Policy development calls for public health to serve the public interest in developing comprehensive public health policies (Turnock, 2012) in order to protect and improve public safety and health. When the assessment of the health of the population is performed, scientific data are collected and analyzed in the form of epidemiologic studies. Evaluation of the data is conducted which may suggest policy revisions or entirely new policies (Rowitz, 2013).

Assessment evaluates significant public health issues, so policies and programs can be formed to address the problem. A major issue in need of policy development is the increasing number of antibiotic resistant bacteria. Numerous microorganisms are developing resistance to a number of antimicrobials because of improper use. Many of these organisms are virtually untreatable. It is estimated that 20% to 50% of all antibiotics prescribed in U.S. hospitals are either inappropriate or unnecessary (Core Elements of Hospital Antibiotic Stewardship Program, 2015).

The misuse of antibiotics and the spread of resistance has become a growing public health threat. Many bacterial infections, once treated with simple antibiotics are now causing life-threatening pneumonia and deadly bloodstream infections. TB, once thought of as virtually extinct from the U.S., is now resistant to many of the first- and second-line treatment agents. Many other serious threats from misuse of antimicrobials include adverse drug and allergic reactions, and CDI. Two policy initiatives are described concerning these issues.

CDC Recommendations

Improvement of antibiotic use is an important public health issue and a national priority (White House Forum on Antibiotic Stewardship Convenes Government and Private Sector Leaders Committed to Improving Antibiotic Prescribing, 2015). The 2006 CDC and the Healthcare Infection Control Practice Advisory Committee (HICPAC) (Siegel, J.D., Rhinehart E., Jackson, M. & Chiarello, L., 2006) guideline stated that control of MDRO in healthcare had, to that point, not been addressed to any extent. To confront this issue there "must include attention to judicious antimicrobial use" (Siegel, et al., 2006). As a result, the "Get smart for Healthcare Campaign" in 2009 encouraged healthcare providers, hospital administrators, patients, and policy makers to promote more efficient use of antibiotics. This campaign also initiated the use of ASPs in acute care hospitals (Get Smart Programs and Observations, 2006). In 2013, the CDC promoted improvement of antibiotic use for resistant bacterial threats in hospitals and communities in the U.S. (Antibiotic Resistance Threats in the United States, 2013). Finally, the document of Hospital Antibiotic Stewardship" (Core Elements of Hospital Antibiotic Stewardship Program, 2015) lists the essential elements necessary for a successful ASP. These are displayed in Table 2.2.

There is significant promise of improved antibiotic use due to an ASP. Quality of patient care has improved due to antibiotic stewardship shown by a better infection cure rate and

Table 2.2

Core Elements of an Antibiotic Stewardship Program

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

(Core Elements of Hospital Antibiotic Stewardship Program, 2015) correct antibiotic therapy (Gross, R., Morgan, A.S., Kinky, D.E., Weiner, M., Gibson, G. A., & Fishman, N.O, 2001). Significant reduction in hospital rates of CDI (*CDC's Top Ten: 5 Health Achievements in 2013 and 5 Health Threats in 2014,* 2014, 2015) and antibiotic resistance is due to the ASP. However, a study (Levin et al, 2012) in 2014 examined the antibiotic prescribing habits of physicians. They reviewed medical records from 183 hospitals and found that antibiotic prescribing potentially could be improved by 37.2%. Policies are needed to guide, and necessitate the development and utilization of this type of program in all acute care and healthcare facilities.

White House National Action Plan

In September 2015, the U.S. government and the White House issued the "National Action Plan for Combating Antibiotic-Resistant Bacteria" (*National Action Plan for Combating Antibiotic-resistant Bacteria*, 2015). This document is a roadmap to guide the nation in confronting this challenge. Its vision is to "work domestically and internationally to prevent, detect and control illness and death related to infections caused by antibiotic-resistant bacteria by implementing measures to mitigate the emergence and spread of antibiotic resistance and ensuring the continued availability of therapeutics for the treatment of bacterial infections." (White House Forum on Antibiotic Stewardship Convenes Government and Private Sector Leaders Committed to Improving Antibiotic Prescribing, 2015). Five goals are included in this National Action Plan (NAP): 1) slow the emergence of antibiotic resistance; 2) strengthen surveillance of resistance bacteria; 3) develop rapid diagnostic tests; 4) increase new antibiotic and vaccine development; and 5) collaborate internationally on these issues (White House Forum on Antibiotic Stewardship Convenes Government and Private SectorLeaders Committed to Improving Antibiotic Prescribing, 2015).

Goal 1 of the National Action Plan: slow the emergence of antibiotic resistance.

Goal 1 of the NAP calls for the direct and essential action to be taken in the judicious use of antibiotics. Implementation of an ASP for all medical facilities where the prescribing of antibiotics is prominent is recommended. Judicious use of antibiotics in healthcare slows the. emergence of resistance and extends the effectiveness of antibiotics. The goal is that each patient ***"receives the right antibiotic at the right time at the right dose for the right duration…"*** (White House Forum on Antibiotic Stewardship Convenes Government and Private Sector Leaders Committed to Improving Antibiotic Prescribing, 2015).

The significant outcomes of this goal from the NAP 2015 include 1) the establishment of an ASP in all acute care hospitals with improved antibiotic stewardship across all healthcare settings; 2) reduction of inappropriate antibiotic use by 50% in outpatient settings and by 20% for inpatients; and 3) establishment of antibiotic resistance prevention programs in all 50 states (White House Forum on Antibiotic Stewardship Convenes Government and PrivateSector Leaders Committed to Improving Antibiotic Prescribing, 2015). The utilization of an ASP is needed to meet the goals of the National Action Plan and to reduce the increasing public health burden of antibiotic resistant bacteria.

Goal 2 of the National Action Plan: strengthen surveillance of resistance bacteria.

Improved detection and control of antibiotic resistance is needed. A coordinated effort will be able to monitor pathogens for resistance in all hospitals, eventually branching out to other healthcare settings. These activities will monitor the usage of antimicrobials and their resistance patterns, thus enhancing surveillance.

Goal 3 of the National Action Plan: develop rapid diagnostic tests.

Rapid detection of resistant bacterial infections enhances treatment by decreasing inappropriate antibiotic use. An expedited response from the microbiology lab provides more optimal treatment decisions. Classic microbiology cultures have at least a two-day lag-time before results are finalized. However, rapid, nucleic acid-based tests provide results in only hours. (Dellit, et al., 2007) Use of these quicker testing procedures, and research to develop even more efficient ones, is greatly needed to enhance ASP efforts.

Goal 4 of the National Action Plan: increase new antibiotic and vaccine development.

There is an urgent need for new antibiotics. Currently, there are few new antibiotics in the pipeline. Advancement of drug development is in need from scientific research to generate new antibiotics. Incentives are proposed for research in the development of antibiotics. Clinical trials to test their efficacy and safety are also need. These trials must be made more efficient to expedite the introduction of new antibiotics for therapy

Goal 5 of the National Action Plan: collaborate internationally on these issues.

Antibiotic resistance is not only a problem in the U.S., it is an international problem. No nation, including the U.S. is isolated from resistant bacteria. Thus, ASPs are needed worldwide. To that end, the World Health Organization has developed a program to enhance the detection, analysis, and reporting of antimicrobial use and resistance. (White House Forum on Antibiotic Stewardship Convenes Government and PrivateSector Leaders Committed to Improving Antibiotic Prescribing, 2015) The U.S. supports this international collaboration in the fight against antibiotic resistance.

Assurance

Assurance, the third core function of public health, ensures that services are delivered. Once an action plan has been initiated, assurance is utilized to ensure that a program is implemented as planned. Lastly, the program is evaluated for effectiveness and whether it needs to be reformed or redirected (Turnock, 2012).

Measures (usually epidemiologic) are used to analyze data concerning the outcome. For antibiotic stewardship, there are a myriad of measures to evaluate the amount of antibiotic use in hospitals, the amount of antibiotic resistance, and clinical outcomes. The amount of antibiotic use is calculated by two measures: either days of therapy (DOT) or defined daily dose (DDD). DOT is the sum of days any amount of a specific antibiotic is administered to a patient divided by patient days in the hospital (Core Elements of Hospital Antibiotic Stewardship Program, 2015). On the other hand, DDD is the amount of drug delivered to the patient divided by a standard developed by the World Health Organization (Core Elements of Hospital Antibiotic Stewardship Program, 2015). Examples of calculations are shown in table 2.3. Other measurements include total hospital antibiotic use, targeted antibiotic use, and duration of therapy.

One way to measure the impact of antibiotic stewardship is by focusing on patients who recovered from antibiotic-resistant infections. These patients, under the influence of an ASP, are monitored to assess the percentage of patients who recovered from all hospital infections, the percentage of patients who developed a “super” infection, and those who died from the infection.

Clinical outcomes are a major measure of assurance for antimicrobial usage. With changing therapy recommended by the ASP, measures are needed to assure physicians that replacing an antibiotic for one preferred by the ASP is clinically efficacious, safe, and preserves valuable antimicrobials. Clinical outcome measures for this purpose include all-cause mortality, infection-related mortality, duration of hospitalization, and rate of readmission (Kollef, M.H. & Kollef, K.E.,2011). Clinical cures or improvement can also be measured. These studies

Table 2.3

Examples of Defined Daily Dose and Days of Therapy Calculations

Define Daily Dose (DDD)

Calculation of yearly rates

Annual amount of antibiotics dispensed in 1996:

26,916,839 DDD

Population (from Census): 3,959,698

26916839 DDD/3,959,698 = 6.80 DDD/inhabitant-year

6.80 x 1000/365 = **18.63 DDD/1000 inhabitant-days**

Days of Therapy

2009 Pharmacy drug budget of $3,000,000
Antimicrobial acquisition costs $750,000 (25% of budget)

Cost savings (percent reduction in antimicrobial costs):

a) overall antibiotic acquisition costs
2010 $750,000
2011 $675,000

Absolute decrease of $75,000, equals 10% reduction

b) ICU antibiotic acquisition costs
2010 $100,000 (patient days = 2000, $50/patient-day)
2011 $75,000 (patient days = 2000, $37.50/patient-day)

Absolute decrease of $25,000, equivalent to a reduction of $12.50/patient-day

Adapted from Public Health, Ontario, Antimicrobial Stewardship Programs.

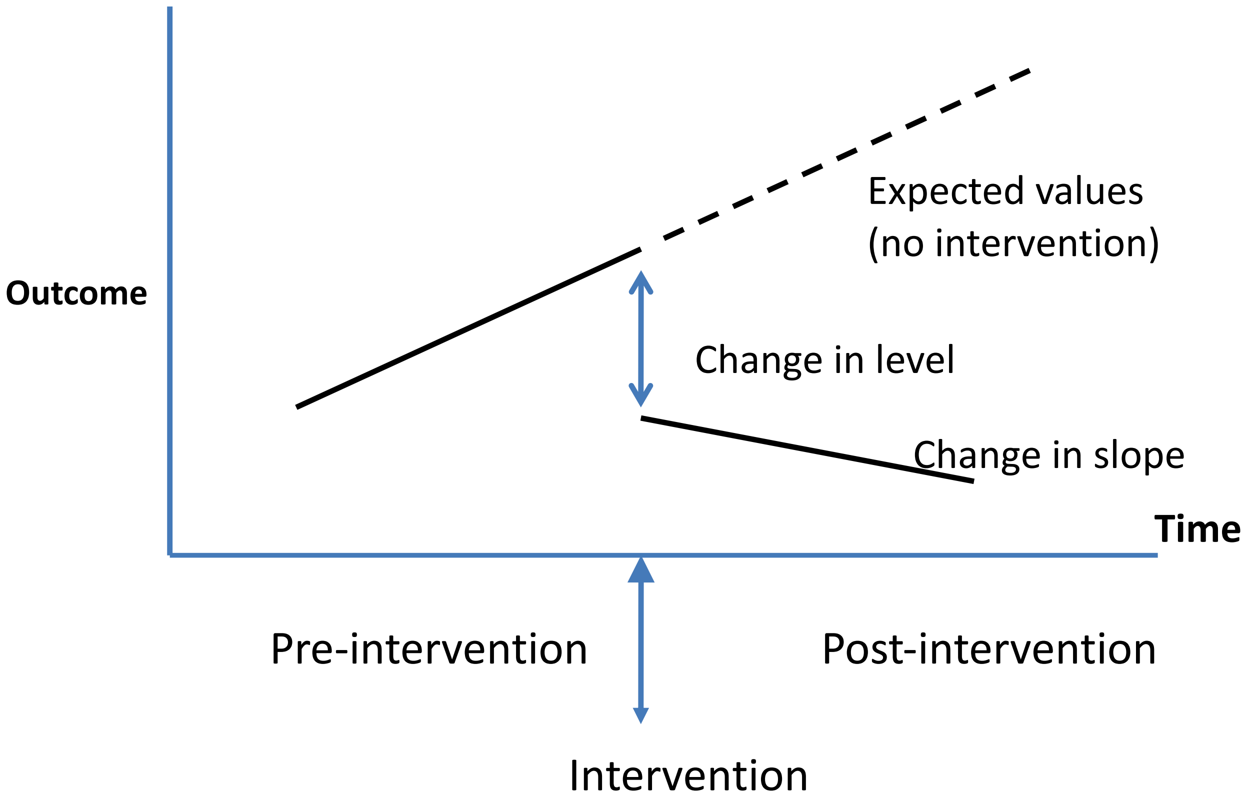
sometimes cannot be sufficiently powered as larger studies are needed. These larger studies will ensure the validity of the intervention.

Microbiologic outcomes can also demonstrate the validity of an ASP. This can be measured by the percentage of organisms resistant to a certain antibiotic, the percentage of drug-resistant organisms, or the number of infections due to a particular drug-resistant organism (MacDougal, C. & Polk, R.E., 2005). However, there are other factors attributable to ASPs that can affect resistance. The rate of isolation of resistant bacteria in the selection of antimicrobials, duration of therapy, and dosage of specific antibiotics can all be a factor. These all affect resistance patterns. However, in spite of the desire to associate microbiology data and resistance, inferring patient improvement with microbiological results can be inaccurate (Phillips, 2001).

A study by Ansari and colleagues (Ansari, F., Gray, K., Nathwani, S., Ogston, S., Ramsay, C. & Davey, P., 2003) examined various endpoints of an ASP for changes in antimicrobial usage and antibiotic resistance to test the program's effectiveness in the hospital. The study analyzed multiple time points prior to and subsequent to the initiation of the stewardship program. Figure 2.2 displays a graph of the results of the study with outcomes (shown on the y-axis) and time before and after intervention (on the x-axis). This depicts an increase in antibiotic use and resistance, and shows an increasing slope before antibiotic stewardship intervention. The graph also displays an extrapolated (dashed) line which depicts the situation had the intervention not been started. At the point of initiating antibiotic stewardship, a gradual decrease in the line's slope illustrates a reduction in antibiotic use and resistance. From the data of antibiotic use and antibiotic resistance, a significant decrease in the slope is a positive sign of the effectiveness of an ASP. These results exemplify how measuring key outcomes can assure the success of an ASP.

Figure 2.2

Graph Depicting Successful Antibiotic Stewardship



(Adapted from Ansari, F., Gray, K., Nathwani, S., Ogston, S., Ramsay, C. & Davey, P. 2003)

Assurance determines the fate of an intervention. Outcomes of assurance can recommend a continuation of the program with potential minor changes, complete program revamping, or the end of the program. Assurance compares what is needed to what is delivered by a program. It is a valuable evaluation of an ASP. Ineffective public health programs waste valuable monetary resources, and lead to diminished health and increased mortality.

Increased antibiotic resistance is a growing public health issue and ASPs in hospitals are necessary to reverse this alarming trend. Measurements to analyze successes and failures are required for the ultimate accomplishments of the program. The amount of antibiotics used, recovery from infection, clinical outcomes, and microbiological outcome can be measured. However, the results of each outcome measure can have varying validity. Use of these measures assures that the antibiotic stewardship program is performing appropriately.

As shown by the variety and increasing number of urgent and serious bacterial threats to our health, a concerted effort is needed by all hospital personnel, under the guidance of the ASP, to prevent the continued rise in antibiotic resistance. Monitoring and directing antibiotic therapy, the main mission of an ASP, is needed to assure healthy patient outcomes and reduced antibiotic resistance. All medical facilities need to have a well-functioning ASP for the health and safety of its patients.

CHAPTER 3

LEADERSHIP, EDUCATION, AND FUTURE RESEARCH

Leadership

Leadership is critically needed for the success of an ASP. The leaders must be dedicated to the program interventions and can contribute in a number of ways. Leadership can issue formal statements supporting the efforts of the ASP to improve and monitor antibiotic usage. Leaders can add antibiotic stewardship-related duties to job descriptions and annual performance reviews to encourage compliance by clinical personnel. Staff in departments relevant to antibiotic stewardship should be given sufficient time to implement activities of the program (Core Elements of Hospital Antibiotic Stewardship Program, 2015). Also, support for training and education should be provided. Besides these, the dedication of financial, human, and IT resources to the ASP greatly enhances its effectiveness (Core Elements of Hospital Antibiotic Stewardship Program, 2015). For any ASP to succeed, support from the administration is crucial.

Program funding, institutional policy, and physician autonomy are issues that must be addressed by hospital leaders in the development of an ASP. The duty of administrators is to deliver answers to these critical issues. Funding of the program is an absolute must for the initiation and continuation of the ASP. Infectious disease doctors and clinical pharmacists must be compensated, and information technology must be kept up-to-date. However, leadership can show how these expenses can be covered by the savings procured by activity of the stewardship program that reduce hospital expenses.

Physician autonomy for prescribing in the past has allowed physicians to use the antibiotic of their choice to treat an infection. Policies are needed to change this, and the antibiotic prescribing habits of physicians via ASPs. Administration needs to enact this policy or physicians will continue inappropriate antibiotic therapy, derailing the ASP (Dellit, et al., 2007) and extending the perilous cycle of antibiotic resistance.

Education

The CDC offers many documents and websites concerning antibiotic-resistant bacteria and ASPs. These documents advise the initiation of an ASP and the continuation of that program. Descriptions of antibiotic–resistant threats to hospital patients are available. The U.S. government has also issued a policy paper that emphasizes goals to be met concerning resistant bacteria (White House Forum on Antibiotic Stewardship Convenes Government and PrivateSector Leaders Committed to Improving Antibiotic Prescribing, 2015).

In addition to the CDC information about resistance and ASPs, there is a need for more education of physicians, other healthcare providers, and hospital staff about antibiotics stewardship (Core Elements of Hospital Antibiotic Stewardship Program, 2015). Healthcare providers must be enlightened about their contributions to the problem of antibiotic resistance. Old prescribing habits must be broken, and new, improved antibiotic treatments that decrease the chance of resistance must be adopted hospital-wide. However, education alone, without the acceptance of formulary restriction or preauthorization interventions, shows minimal effect (Dellit et al., 2007).

Regular updates about antibiotic prescribing and antibiotic resistance should be provided to inform the clinical staff about state and national trends in antibiotic resistance (Core Elements of Hospital Antibiotic Stewardship Program, 2015). Facility-specific results are also analyzed and then shared with pertinent hospital personnel. There are other forms of education concerning resistance and ASPs that can be utilized. Presentations in formal and informal settings provide a means to further promote stewardship intervention. Posters, flyers, newsletters, and electronic communication are other effective means of educating about antibiotic issues.

Another reason why education is needed for prescribing and antibiotic resistance is the limited time medical schools spend teaching about infectious diseases or the antibiotics to treat infections (MacDougal, C. & Polk, R.E., 2005). Consequently, what physicians learned on these subjects has been gleaned from colleagues, antibiotic handbooks, and pharmaceutical sales representatives (MacDougal, C. & Polk, R.E., 2005). Also, most physicians are cognizant of the antibiotic resistance issue that exists; however, they underestimate the true scope of the problem, especially in their own facility (MacDougal, 2005) With limited knowledge of antibiotic resistance, physicians and other health care providers may be open to education about remedies to this issue and the value of an ASP.

Future Research

Antibiotic stewardship is a relatively young discipline. Thus, there are many areas of research that can improve the outcomes. One area that needs study involves the two primary forms of intervention: formulary restriction and preauthorization or prospective audit with intervention and feedback. A determination is needed as to which active intervention generates the best results to decrease antibiotic resistance in hospitals.

Along with primary interventions, supplemental strategies are also utilized in ASPs. These strategies, such as guidelines and clinical pathways and computer surveillance and decision support will always need improvement to enhance their capability. These interventions can only be executed with IT support. Research is needed to further develop these systems to better serve ASPs needs to perform these interventions. Other secondary interventions also need studied to determine if they can be improved, and better complement primary interventions effectively. Both primary and secondary interventions can be utilized as ASP strategies. Alone, secondary interventions are not nearly as successful as a primary intervention. However, both primary and secondary strategies, when implemented together, are more effective. Research is needed to elucidate which of the primary and secondary strategies when implemented together, yield the most successful results.

ASPs were initially implemented in adult healthcare settings. Research is needed to better utilize ASP effectiveness in other different healthcare settings. Hospitalized children are an area of concern. Many children's hospitals are implementing or developing an ASP (Newland, J.G., Gerber, J.S., Weissman, S.S., Shah, S.S., Turgeon, C., Hedican, E.B….& Hersh, A.L, 2015). Analysis of the ability of an intervention to produce positive outcomes and reduce antibiotic resistance in settings other than adult health care requires further investigating.

Institutional policies are needed to establish ASPs in the hospital. Leadership support from the hospital administration is necessary for the success of the policy for these programs. Education, a supplemental strategy of antibiotic stewardship, supports the advancement of ASPs, and can fill in the gaps in clinical personnel knowledge of prescribing antibiotics and bacterial resistances.

Research on primary and secondary interventions of an ASP is necessary to establish which ones are more successful, and which combinations can be established as effective. The efficacy of ASP in outpatient situations needs to be researched. Nonetheless, antibiotic stewardship will always require research for advancement of the program so it can continue to decrease inappropriate antibiotic use, and reduced antibiotic resistance.

CHAPTER 4

CONCLUSIONS AND RECOMMENDATIONS

The three core functions of public health ultimately direct interventions for the betterment of the health of the community and the nation. Assessment, the first of the core functions, has the role of discovering the health needs of the public. Using a variety of tools and depending upon the health issue, public health problems are exposed from the data uncovered by assessment. Assessment directs policy development. Policies are then formulated and supported by the assessment results and community needs. In the policy development step, programs are formed to address the issues. These programs are subsequently evaluated to assure they are delivering what the policy promises. The end results of the assurance step can decide the fate of the program, whether to continue with the status quo, create changes, or reassess the health issue.

Antibiotic resistance has been shown to be a public health threat for many years, perhaps naively ignored. Since the beginning of antibiotic treatment, bacteria have evolved and resistance has occurred. Subsequent introduction of other antibiotics have exhibited the same results. By the 1970s, *S. aureus*, an invasive bacteria, became resistant to methicillin and other similar drugs, and gram negative bacteria (i.e.—*E. coli, K. pneumoniae*)started to become resistant to multiple drugs. By the mid-1990s, Enterococci were resistant to vancomycin, a drug of last resort. By the early 2000s, there was a significant rise in the number of concerning drug resistant organisms, and today where several bacteria are now becoming untreatable by any of the available drug treatments.

With significant increases in antibiotic resistance, a public health intervention was necessary to stop this surge of antibiotic resistance. Appropriate use of antibiotics was the answer. For this, hospitals initiated an ASP to restrict improper antibiotic use. Data from these initial studies of antibiotic stewardship showed a significant decrease in antimicrobial use and inappropriate prescribing. Other metrics also displayed a favorable assessment of stewardship. Hospital policies followed. Then, in 2014, the U.S. government and the White House developed the "National Action Plan for Combating Antibiotic-resistant Bacteria" with the goal of decreasing resistant bacteria. The primary goal of this policy is the establishment of an ASP in all hospitals and other medical facilities nationwide.

The CDC offers many documents and websites concerning antibiotic-resistant bacteria and ASP. These documents provide guidance for the initiation of an ASP and the continuation of that program. Descriptions of antibiotic–resistant threats to hospital patients are available. The U.S. government has also issued a policy paper that emphasizes goals to be met concerning resistant bacteria.

A public health intervention assesses community health issues, develops policies to remedy the issue, and assures effective outcomes of a program. These are the three core functions of Public Health. These can be used to analyze antibiotic stewardship response to antibiotic resistance. This process ensures proper antibiotic use with a clear decrease in antibiotic resistant bacteria.

ASP is the answer to antibiotic resistance. The Core Functions of Public Health—Assessment, Policy Development and Assurance—show how effective antibiotic stewardship can be. Hopefully, ASP will be in all hospitals to fight this major public health issue of our time.

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