REPORT 3 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (I-15)
Combating Antibiotic Resistance: An Update
(Reference Committee K)

EXECUTIVE SUMMARY

Objective. To provide an overview of the global public health threat of antibiotic resistance and the range of actions being taken to address the problem, including actions physician can take to promote the stewardship of current antibiotics.

Methods. English-language articles were selected from a search of the PubMed and Google Scholar databases from January 2010 to June 2015 using the search terms “antimicrobial resistance,” “antibiotic resistance,” “antimicrobial stewardship,” and “antibiotic stewardship” in the article title and/or abstract. Internet sites managed by federal agencies, relevant public health organizations, foundations, and advocacy groups were also reviewed. Additional articles were culled from the reference lists contained in the pertinent articles and other publications. Additionally, this report considers and expands upon information presented in previous AMA reports on antibiotic resistance including: Council on Scientific Affairs (CSA) Report 3-A-00 Combating Antibiotic Resistance Via Physician Action and Education: AMA Activities, and Board of Trustees Report 20-A-12 Enhancing Antibiotic Stewardship in the Inpatient Setting to Improve Patient Outcomes.

Results. The Centers for Disease Control and Prevention (CDC) estimates that at least 2 million people in the U.S. acquire serious bacterial infections that are resistant to one or more antibiotics and at least 23,000 people die each year as a direct result of these antibiotic-resistant infections. While the decline in effectiveness of current antibiotics is alarming, we are also facing a decline in the development of new antibiotics due in part to the withdrawal of most major pharmaceutical companies from the antibiotic market. This report outlines the recent engagement by the federal government on antibiotic resistance and discusses actions taken to accomplish the goals of the National Strategy for Combating Antibiotic Resistance. These goals include: slowing the emergence of resistant bacteria through antibiotic stewardship programs across both human health and agricultural settings; strengthening public health and animal health surveillance efforts to combat resistance; promoting the development and use of rapid diagnostic tests for the identification and characterization of resistant bacteria; and accelerating research and development for new antibiotics.

Conclusion. Antibiotic resistance poses a serious threat to the health of the public and therefore, a coordinated, multi-sector, and multi-pronged approach is required to address the issue. Efforts need to be taken by both human health and animal health sectors to promote the adoption of antibiotic stewardship programs. Patients need to continue to be educated regarding the appropriate use of antibiotics. Incentives are needed to encourage the development of new antibiotics as well as infectious disease diagnostics. Public health and veterinary health systems need to be funded adequately to conduct systematic surveillance of antibiotic resistance and use so we have a better understanding of the problem and can work to prevent the spread of infections.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 3-I-15

Subject: Combating Antibiotic Resistance: An Update

Presented by: Louis J. Kraus, MD, Chair

Referred to: Reference Committee K
(Hillary Johnson-Jahangir, MD, Chair)

INTRODUCTION

This is a further report on a Council on Science and Public Health (CSAPH) initiative to address the global public health threat of antibiotic resistance and promote stewardship activities. The Council previously issued two reports on this topic, both in 2000. The first discussed antibiotic resistance as a major public health concern and outlined the AMA's activities to address the issue. The second report addressed the use of antimicrobials in consumer products. Since that time, the Board of Trustees issued a report in 2012 on antibiotic stewardship activities to improve patient outcomes in the inpatient setting, and the House of Delegates also has adopted a number of related policies.

This report provides an update on the status of antibiotic resistance in the United States (U.S.) and addresses the use of antibiotics in humans and food-producing animals, the development of new antibiotics, public health surveillance, and infectious disease diagnostics.

METHODOLOGY

English-language articles were selected from a search of the PubMed and Google Scholar databases from January 2010 to June 2015 using the search terms "antimicrobial resistance," "antibiotic resistance," "antimicrobial stewardship," and "antibiotic stewardship" in the article title and/or abstract. Internet sites managed by federal agencies, relevant public health organizations, foundations, and advocacy groups also were reviewed. Additional articles were culled from the reference lists contained in the pertinent articles and other publications.

Additionally, this report considers and expands upon information presented in previous AMA reports on antibiotic resistance including: Council on Scientific Affairs (CSA) Report 3-A-00 Combating Antibiotic Resistance Via Physician Action and Education: AMA Activities, and Board of Trustees Report 20-A-12 Enhancing Antibiotic Stewardship in the Inpatient Setting to Improve Patient Outcomes.

BACKGROUND

Antimicrobial resistance (AMR) has been a major public health threat for many years. In fact, Alexander Fleming, in his 1945 Nobel Prize speech for the discovery of penicillin, anticipated that misuse could lead to resistant bacteria. AMR develops when a microorganism (be it a bacterium, fungus, virus, or parasite) no longer responds to a drug to which it was originally sensitive, making

infections harder or impossible to control. This report will focus specifically on the reduced ability of treat human infections based on common bacteria that may develop resistance to antibiotics.

The Centers for Disease Control and Prevention (CDC) estimates that at least 2 million people in the U.S. acquire serious bacterial infections that are resistant to one or more antibiotics and at least 23,000 people die each year as a direct result of these antibiotic-resistant infections.[1] Furthermore, the economic costs of antibiotic resistance to the U.S. are estimated at $20 billion in excess direct health care costs, with additional costs to society for lost productivity estimated to be as high as $35 billion per year in 2008 dollars.[1] In 2013, the CDC assessed threats to human health resulting from antibiotic use and prioritized them into three categories – urgent, serious, and concerning. The urgent threats included *Clostridium difficile*, carbapenem-resistant Enterobacteriaceae (CRE), and drug-resistant *Neisseria gonorrhoeae*.[1]

In 2014, the World Health Organization (WHO) released its first global surveillance report on AMR, which included data from 114 countries.[2] The report noted that the problem of AMR is "so serious it threatens the achievements of modern medicine," as many procedures – including cancer chemotherapy, complex surgery, dialysis for renal disease, and organ transplantation – are dependent upon effective antibiotics. The WHO report warns that "a post-antibiotic era – in which common infections and minor injuries can kill – is a very real possibility."

While the decline in effectiveness of current antibiotics is alarming, a decline in the development of new antibiotics has occurred, as well, due in part to the withdrawal of most major pharmaceutical companies from the antibiotic market. While major reports and initiatives have outlined steps and policies to address the decline in antibiotic innovation, a renewed focus is necessary given the gravity of the situation, and efforts to promote the development of new antibiotic drugs must be devised and implemented.

FEDERAL INITIATIVES

In September of 2014, President Obama issued an Executive Order on the issue of combating antibiotic resistant bacteria, which states that the federal government will "implement measures that reduce the emergence and spread of antibiotic-resistant bacteria and help ensure the continued availability of effective therapeutics for the treatment of bacterial infections."[3] The Executive Order outlined a number of specific actions to be taken to combat antibiotic resistance, including, but not limited to establishing a task force for combating antibiotic-resistant bacteria chaired by the Secretaries of Agriculture, Defense, and Health and Human Services (HHS); improving antibiotic stewardship programs; developing a five-year National Action Plan to implement the *National Strategy for Combating Antibiotic Resistance (National Strategy)*; strengthening national surveillance efforts for resistant bacteria; promoting next generation antibiotics and diagnostics; and establishing the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria.

In conjunction with the Executive Order, the White House released the *National Strategy*, which outlines five goals for action by the U.S. government in collaboration with a wide range of partners.[4] The five goals are: (1) slowing the emergence of resistant bacteria and preventing the spread of resistant infections; (2) strengthening national one-health surveillance efforts to combat resistance; (3) advancing development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria; (4) accelerating basic and applied research and development for new antibiotics, other therapeutics, and vaccines; and (5) improving international collaboration and capacities for antibiotic resistance prevention, surveillance, control, and antibiotic research and development.

Along with the release of the *National Strategy*, the President's Council of Advisors on Science and Technology (PCAST) released its *Report to the President on Combating Antibiotic Resistance.* Key recommendations included in the report focus on antibiotic resistance policy, stewardship, and surveillance. The recommendations fall into three key areas:

- Improving surveillance of antibiotic-resistant bacteria;
- Increasing the longevity of current antibiotics by improving use and implementation of interventions; and
- Increasing the rate at which new antibiotics and other interventions are discovered and developed.[5]

In March 2015, the White House released the *National Action Plan for Combating Antibiotic Resistant Bacteria*, which outlines steps for implementing the *National Strategy* and the policy recommendations contained in the PCAST report. The *National Action Plan* outlines federal activities over the next five years to:

- Enhance domestic and international capacity to prevent and contain outbreaks of antibiotic-resistant infections;
- Maintain the efficacy of current and new antibiotics; and
- Develop and deploy next-generation diagnostics, antibiotics, vaccines, and other therapeutics.[6]

On June 2, 2015, the White House hosted the *Forum on Antibiotic Stewardship* to bring together more than 100 human and animal health leaders involved in antibiotic stewardship. The leaders represented hospitals, health care systems, human and animal health advocates, pharmaceutical companies, agriculture organizations, and others committed to taking part in antibiotic stewardship activities. The purpose was to obtain commitments from key human and animal health constituencies to implement changes over the next five years to slow the emergence of resistant bacteria and prevent the spread of resistant infections.

A number of federal agencies and organizations have taken actions toward accomplishing the goals as set out in the plans above. These actions will be included in the relevant sections of this report.

PREVENTING INFECTIONS

One of the CDC's priorities in addressing antibiotic resistance involves preventing infections to the extent possible. This important step can be accomplished through proven public health strategies including immunizations, hand washing, safe food preparation, keeping water safe, preventing the spread of sexually transmitted diseases, and using antibiotics as directed. While these are important steps that individuals can take, there are also important steps that health care facilities can take to prevent health care-associated infections.[7] Preventing infections not only reduces the spread of drug-resistant bacteria, but it also reduces the need to use antibiotics, thereby decreasing the likelihood of resistance.

STEWARDSHIP OF CURRENT ANTIBIOTICS

Antibiotic-resistant bacteria are a natural consequence of antibiotic use and are the result of mutation and natural selection as well as the transfer of genetic material between species of bacteria. Since each use impacts the lifespan of an antibiotic, tensions exist between the interests of individuals and corporations and the interests of society.[8] Since few new antibiotics are being developed, stewardship programs are especially necessary to help extend the therapeutic life of existing antibiotics.

Stewardship of antibiotics requires identifying the microbe responsible for disease; administering the most effective antibiotic at the appropriate dose, route, and time; and discontinuing antibiotic therapy when it is no longer needed.[1] In order to be effective, stewardship needs to occur across the various settings within the health care system as well as in agricultural settings.

Use in Humans

According to the CDC, the use of antibiotics is the single most important factor leading to antibiotic resistance around the world. Antibiotics are among the most commonly prescribed drugs. However, up to 50% of the instances of antibiotic use either are not necessary or are not optimally effective as prescribed.[1] Examples include prescribing antibiotics without ordering laboratory tests to confirm that bacteria are causing an infection and patients demanding antibiotics for the treatment of conditions caused by viruses, which will not respond to antibiotics. Under-treatment through inadequate doses or inappropriate treatment duration also can result in antibiotic-resistant strains.[8]

Inpatient Setting

Antibiotics are commonly administered to patients in hospitals to treat infections. However, studies have demonstrated that treatment indication, choice of agent, or duration of therapy can be incorrect in up to 50% of the cases in which antibiotics are prescribed.[9] One study reported that 30% of antibiotics received by hospitalized adults outside of critical care were unnecessary, and that antibiotics were often used for longer than recommended or for the treatment of colonizing or contaminating microorganisms.[10] Incorrect prescribing of antibiotics exposes individual patients to potential complications of antibiotic therapy, including infection with *Clostridium difficile*, which often recurs and can progress to sepsis and death. The CDC has estimated that approximately 250,000 *C. difficile* infections occur in hospitalized patients each year.[1]

A number of organizations have developed resources to assist hospitals in developing antibiotic stewardship programs. The CDC's *Get Smart for Healthcare* campaign provides quality improvement tools and assessments for the implementation of stewardship campaigns in the inpatient setting.[11] In September 2015, hospital system members of Premier, Inc., a health care improvement company, announced that they will work to implement at least three elements of the CDC's core elements for antibiotic stewardship programs and will test, measure and track their efforts to reduce the inappropriate use of IV antibiotic combinations by 20 percent.[12]

California is the only state that requires hospitals to have stewardship programs. In 2006, California enacted SB 739, requiring acute care hospitals, by January 2008, to develop a process for evaluating the judicious use of antimicrobials. A 2010-2011 survey of acute care hospitals in the state found that 50% reported a current antibiotic stewardship program, 30% reported planning a stewardship program and 20% reported not having or being unsure of whether they had one.[13] In 2014, California strengthened its law to require acute care hospitals to adopt and implement an antibiotic stewardship program in accordance with guidelines established by the federal government and professional organizations that includes a process to evaluate the judicious use of antibiotics. The law also requires the hospitals to develop a physician-supervised, multidisciplinary antimicrobial stewardship committee and requires the reporting of program activities to hospital clinical quality improvement activities.[14] It is too early to evaluate the overall effects of these changes.

In 2014, the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) presented the evidence base to CMS to demonstrate how

adopting antimicrobial stewardship as a Condition of Participation would improve patient care and health outcomes, as well as lower health care costs associated with antibiotic overuse, infectious and antimicrobial resistance.[15] In 2015, CMS confirmed that it plans to propose a Condition of Participation for antibiotic stewardship, with an implementation window in 2017.

Outpatient Setting

Using the IMS Health Xponent database, the CDC analyzes prescribing data to understand trends in outpatient oral antibiotic prescribing and to identify interventions to improve prescribing. In 2011, health care providers prescribed 262.5 million courses of antibiotics, or 842 prescriptions per 1,000 persons.[16] Penicillin and macrolides were the most common categories prescribed, with the most frequently prescribed agent being azithromycin. Rates of prescribing vary by state and also are higher in the southern U.S. and lower in the western states (Figure 1). Family practitioners prescribed the most courses of antibiotics (24%).[16] Non-physician prescribers (dentists, nurse practitioners, and physician assistants) were responsible for nearly the same number of antibiotic prescriptions as family physicians. Dentists alone are responsible for 10% of antibiotic prescribing.[16] Accordingly, a number of provider groups exist for targeted education.

In response to documented inappropriate prescribing and rising rates of resistance, the CDC launched in 1995 the *National Campaign for Appropriate Antibiotic Use in the Community*. In 2003, the campaign was re-branded and launched as the *Get Smart: Know When Antibiotics Work* campaign, to improve antibiotic prescribing and use in both the inpatient and outpatient settings. The program includes evidence-based recommendations and clinical practice guidelines for the treatment of common infections in adults (acute rhinosinusitis, acute uncomplicated bronchitis, common cold or non-specific upper respiratory tract infection, pharyngitis, and acute uncomplicated cystitis) and children (acute rhinosinusitis, acute otitis media, pharyngitis, common cold or non-specific upper respiratory tract infection, bronchiolitis, and urinary tract infections).[17]

In 2012 the American Board of Internal Medicine Foundation launched *Choosing Wisely*® with a goal of advancing a national dialogue on avoiding wasteful or unnecessary medical tests, treatments and procedures. More than 70 specialty society partners have released recommendations with the intention of facilitating wise decisions about the most appropriate care based on a patient's individual situation; 27 of these recommendations are related to the appropriate use of antibiotics (see Appendix B).[18]

Long-term Care Setting

Antibiotics are commonly prescribed medications in nursing homes. Up to 70% of long-term care facility residents receive an antibiotic at least once per year and estimated costs of antibiotics in this setting range from $38 million to $137 million per year.[19] Up to 75 % of antibiotics prescribed in nursing homes are prescribed incorrectly, either because the drug is unnecessary or the prescription is for the wrong drug, dose, or duration.[20, 21] Many long-term care residents are "colonized" with bacteria, meaning that germs can live on the skin, wound surfaces or even in the bladder without making the person sick. While colonization with bacteria that can also lead to true infection is not limited to the long-term care setting, the difficulty of distinguishing colonization from true infection in this vulnerable population is a challenge which can contribute to antibiotic overuse.

In July 2015, CMS issued a proposed rule that would revise the requirements Long-Term Care facilities must meet to participate in the Medicare and Medicaid programs. The rule proposes that a facility's Infection Prevention and Control Plan (IPCP) must include an antibiotic stewardship

program that includes antibiotic use protocols and systems for monitoring antibiotic use and recording incidents identified under the facility's IPCP and the corrective actions taken by the facility.[22] The CDC also has advised all nursing homes to improve antibiotic prescribing practices and reduce their inappropriate use and has released a resource on the *Core Elements of Antibiotic Stewardship for Nursing Homes*.[23]

Telemedicine

A study comparing antibiotic prescribing at e-visits and office visits for both sinusitis and urinary tract infection (UTI) found that prescribing rates were higher at e-visits, particularly for UTIs. The researchers concluded that when physicians are unable to directly examine the patient, they may use a "conservative" approach and order antibiotics.[24] At least one rural California hospital has found that telemedicine-based antimicrobial stewardship programs can improve prescribing and reduce bacterial resistance to antibiotics. Key elements of the program delivered via telemedicine by an offsite infectious disease specialist included ongoing monitoring of prescribing habits combined with various educational initiatives, such as daily reviews of orders for certain classes of drugs, weekly infectious disease rounds, and periodic presentations and discussion at department meetings.[25]

Use in Animals

The use of antibiotics for non-medical purposes in the production of livestock and poultry has been common practice for more than 50 years. Today, 80% of all antibiotics sold in the U.S. are for use in livestock and poultry. The FDA reported that in 2012 more than 32 million pounds of antibiotics sold in the U.S. were for food-producing animals, a 16% increase since 2009.[26] Use in animals often is for preventing infections and for production purposes such as promoting growth, rather than for treating illness.

In 1970, the FDA established a task force to undertake a comprehensive review of the use of antibiotics in animal feed. The task force concluded that "the use of antimicrobials in food-producing animals, especially in sub-therapeutic amounts, was associated with the development of resistant bacteria."[27] In 1977, the FDA proposed to withdraw new drug approvals for sub-therapeutic uses of penicillin and tetracyclines in animal feeds on the grounds that their use for these purposes was not safe and that these drugs were of importance to human medicine. In anticipation of initiating withdrawal proceedings, the FDA issued notices of opportunity for hearing (NOOHs) to all pharmaceutical manufacturers selling the drugs. However, Congress encouraged the agency to delay hearings until there was additional scientific research on the issue. A number of key reports and peer-reviewed studies have been published.[27] According to the CDC, there is a "compelling body of evidence to demonstrate this link between antibiotic use in animals and the resistance from antibiotics."[28]

In 2011, consumer advocacy groups filed a lawsuit against the FDA arguing in part that 21 U.S.C. § 360b(e)(1) compelled the Agency to hold the hearings as previously proposed. The 2nd Circuit Court of Appeals upheld the FDA's decision to not move forward with hearings addressing the withdrawal of FDA approval of the use of these drugs in food-producing animals.[29] In 2012, the FDA released Guidance for Industry (GFI) #209, which includes two principles regarding the judicious use of medically important antimicrobial drugs in food-producing animals. Principle 1 stated "[T]he use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health." Principle 2 stated "[T]he use of medically important antimicrobial drugs in food-producing animals should be limited

to those uses that include veterinary oversight or consultation." It should be noted that the FDA's GFI recommendations are nonbinding.

In 2013, the FDA released GFI #213, which outlines a detailed process and timeline for the implementation of GFI #209.[30] GFI #213 recommends changing the status for medicated feed products from over the counter (OTC) to veterinary feed directive (VFD) and the status for medicated drinking water products from OTC to prescription. That same year, the FDA also issued a proposed VFD. The final VFD rule, issued in 2015, outlines the process for authorizing use of VFD drugs (animal drugs intended for use in or on animal feed that require the supervision of a licensed veterinarian) and provides veterinarians in all states with a framework for authorizing the use of medically important antimicrobials in feed when needed for specific animal health purposes.[31]

A number of high-profile food producers have moved to limit the routine use of medically important antibiotics in food producing animals due to increased consumer demands. In March 2012, the Consumer Reports National Research Center conducted a nationally representative telephone survey about antibiotics in meat products. Eighty-six percent of consumers polled indicated that meat raised without antibiotics should be available in their local supermarket and 72 percent were extremely or very concerned about the overuse of antibiotics in animal feed.[32]

In 2014, Perdue Farms, a major poultry producer, eliminated the routine use of human antibiotics in its chicken production (hatchery and farms). It is now focused on reducing the use of animal-only antibiotics.[33] Tyson Foods, another major poultry producer, has reduced the use of human antibiotics in its broiler chickens by more than 80 percent since 2011 and has eliminated use in its 35 hatcheries. Tyson Foods hopes to eliminate the use of human antibiotics completely in broiler chicken production by September 2017. It also is discussing ways to reduce the use of human antibiotics in its beef, pork, and turkey farms.[34]

Retailers such as Walmart and Sam's Club have adopted policies calling for the judicious use of antibiotics, to treat animals that are ill or at risk, and calling for enhanced veterinary oversight.[35] McDonald's has committed to stop using important human antibiotics in the production of chicken for McDonald's USA by March 2017.[36] Chipotle Mexican Grill, a restaurant chain, has adopted a policy stating that "there's no place for nontherapeutic antibiotics and synthetic hormones on the farms that produce our ingredients."[37]

A smaller group of retail stores, restaurants, and schools are moving toward a "no antibiotics ever" (NAE) policy. In addition to prohibiting the use of medically-important antibiotics, NAE policies also prohibit the use of animal-only antibiotics as well as the therapeutic use of antibiotics in food-producing animals. The Chick-fil-A restaurant chain announced in 2014 that it would move 20 percent of its poultry supply to an NAE policy for 2015. It is working to make its entire poultry supply antibiotic-free by 2019.[38] Whole Foods Market, a national chain of retail grocery stores, has similarly adopted an NAE policy for all fresh and frozen meat products as well as prepared foods.[39] The Urban School Food Alliance, a collaboration of food and nutrition professionals working in major U.S. school districts, has plans to make NAE chicken the new norm in the lunchrooms of the six largest public school districts in the country.[40]

While the pressure to eliminate the use of antibiotics in animal production has led to voluntary changes in the chicken industry, other meat industries have been slower to respond. This is in part because chickens produced for food have shorter lifespans than cattle. But even more importantly, commercial poultry companies have vertically integrated production systems so making changes in

order to reduce antibiotic use is easier as compared to other industries, which involve purchasing products from independent farmers.[41]

The American Veterinary Medical Association's (AVMA) current position statement is as follows: "When the decision is reached to use antimicrobials for treatment, control, or prevention of disease, veterinarians should strive to optimize therapeutic efficacy and minimize resistance to antimicrobials to protect public and animal health and well-being."[42]

SURVEILLANCE

Public health surveillance is the "ongoing, systematic collection, analysis, and interpretation of health data, essential to the planning, implementation and evaluation of public health practice, closely integrated with the dissemination of these data to those who need to know and linked to prevention and control."[43] Surveillance is essential to the early detection of antibiotic-resistant bacteria as well as the rapid response to prevent the spread between patients, within facilities and into communities. Improved surveillance will help identify where resistant infections originate, practices that contribute to emergence, and how resistant microbes are being transmitted.[1]

Currently multiple platforms are being used to track antibiotic resistance, antibiotic-resistant infections, and antibiotic use in humans. Among surveillance systems are the Emerging Infections Program, of which Antibacterial Core Surveillance is a core component; the National Antimicrobial Resistance Monitoring System (NARMS); the National Healthcare Safety Network (NHSN); the Gonococcal Isolate Surveillance Program; and the National Tuberculosis Surveillance System. In August 2015, the CDC launched NARMS Now: Human Data, an interactive tool that contains antibiotic resistance data from bacteria isolated from humans. This tool helps determine how antibiotic resistance has changed over the past 20 years for four bacteria transmitted commonly through food—*Campylobacter*, *E. coli* O157, *Salmonella*, and *Shigella*.[44]

Separate surveillance systems exist to collect data on antibiotic use and resistance in animals. These systems include the National Animal Health Monitoring System (NAHMS), the National Animal Health Laboratory Network (NAHLN), and the Veterinary Laboratory Investigation and Response Network (Vet-LIRN). In May 2015, the FDA proposed to change the reporting requirements for new antimicrobial animal drug sponsors to incorporate species-specific drug sales and distribution data so that the agency could better monitor trends in antimicrobial resistance stemming from foodborne bacteria and retail meats and agricultural animals to promote judicious use of medically important antimicrobials.[45]

The PCAST report, *National Strategy*, and *National Action Plan*, the Council of State and Territorial Epidemiologists, IDSA and others have made recommendations to strengthen public health surveillance of antibiotic resistance in the U.S. They include:

- creating a regional public health laboratory network to strengthen capacity to detect resistant bacteria and serve as a specimen repository for facilitating the development of diagnostic tests and treatments
- expanding and strengthening the national infrastructure for public health surveillance and data reporting
- providing incentives for timely reporting of antibiotic resistance and use in all health care settings
- developing, expanding and maintaining capacity in veterinary and food safety labs to conduct standardized antibiotic susceptibility testing and characterize select zoonotic and animal pathogens

- enhancing and monitoring of antibiotic resistance patterns, and antibiotic sales, usage and management practices across the production chain for food animals and retail meat.[6]

DIAGNOSTICS

The development of rapid diagnostic tests that can be used in health care settings to distinguish between viral and bacterial infections as well as to identify bacterial drug susceptibilities could significantly reduce the prescribing of unnecessary antibiotics. In order for these tools to be useful for the clinical management of infectious diseases, they need to be available at the point of care and be cost-effective.[46] The rapid strep test is a good example. However, other tests currently take three days to a week to identify organisms.[46] Efforts are underway at the federal level to evaluate innovative regulatory pathways to foster the development of infectious disease diagnostic tests and develop well-defined reimbursement policies and incentives to encourage their routine use in the clinical setting.[6] In September 2015, the U.S. House of Representatives introduced the Antibiotic and Rapid Diagnostic Research and Development Tax Credit Act of 2015, which would allow a credit against tax for clinical testing expenses for qualified infectious disease drugs and rapid diagnostic tests.[47]

NEW ANTIBIOTICS

A robust antibiotic development pipeline is essential for creating new antibiotics to replace those being lost to antibiotic resistance. In recent years, most large pharmaceutical companies have exited the antibacterial drug market presumably because little incentive exists to develop drugs the use of which will be restricted to a narrow market and the clinical effectiveness of which will likely be lost over time. As a result, government agencies across the world have been examining ways to encourage research and development of new antibacterial products with measures such as intellectual property extensions, tax incentives, modifications to clinical trial processes and identifying private funding for product research and development.[46] In 2010, the IDSA launched the 10 x 20 initiative, a global commitment to develop 10 new antibiotics by 2020.[48]

The FDA Safety and Innovation Act (FDASIA) enacted in 2012, included provisions to encourage the development of antibacterial and antifungal drugs for the treatment of "serious or life-threatening infections." The Title VIII Generating Antibiotic Incentives Now (GAIN) Act designates antibiotic drugs for identified conditions as Qualified Infectious Disease Products (QIDPs), making them eligible for incentives including priority review under the expedited review program for fast track products and, upon approval, five years of marketing exclusivity. From 2000 to 2010, only five new antibiotics were approved for clinical use, but since the approval of the GAIN Act, the pace has accelerated with four new antibiotics approved in 2014 and one approved in 2015.[49]

According to the PEW Charitable Trusts, 36 new antibiotics are currently in the development pipeline. Given the inevitability that some of these drugs will fail to win approval, there are too few drugs in development to meet current and anticipated needs.[50] A number of organizations, including the AMA, have called for a "sustained and multi-pronged strategy to spur industry and investor interest in reinvigorating the antibiotic pipeline."[48]

Innovative screening processes are necessary to identify potential new antibiotics as researchers have already picked the low-hanging fruit. In January 2015, researchers discovered a new antibiotic, teixobactin, in a screen of uncultured bacteria from a soil sample. The antibiotic is active against gram-positive bacteria and was shown to kill *Staphylococcus aureus* and *Mycobacterium tuberculosis* without developing resistance. While there is no guarantee that this isolated finding

will yield an antibiotic that is useful for human health, researchers surmise that the properties of this compound suggest a path towards developing antibiotics that are likely to avoid development of resistance.[51]

Congress is currently considering additional legislative efforts to facilitate the development of antibiotics, including the Limited Population Antibacterial Drug (LPAD) approval pathway. LPAD creates a new regulatory pathway, whereby high-need antibiotics could be approved based on clinical trials with smaller numbers of patients. It is often not feasible for new antibiotics to be developed using traditional, large clinical trials due to the limited numbers of patients with the target infections. Upon approval, the indications for use would be restricted to a narrowly defined specific population of patients for whom the benefits of the drug outweigh the risks.[52] The LPAD pathway was introduced in the House of Representatives as the Antibiotic Development to Advance Patient Treatment (ADAPT) Act. The ADAPT Act was recently included as part of the 21st Century Cures Act (Cures), which has passed the U.S. House of Representatives. Also included in Cures was the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act, which provides for an increase in payments for new antibiotics and anti-fungals associated with infections with high rates of mortality or significant patient morbidity, and that address an unmet medical need.[53] LPAD was introduced in the Senate as part of the Promise for Antibiotics and Therapeutics for Health (PATH) Act; at the time of the preparation of this report, Senate action on this piece of legislation was pending.

AMA ACTIVITIES

Consistent with its policies in this area (see Appendix A), the AMA has advocated for removing barriers to antibiotic development. In 2012, the AMA supported the GAIN Act. In 2014, the AMA supported H.R. 3742, the ADAPT Act. The AMA also supported the inclusion of ADAPT in the 21st Century Cures legislation.

The AMA also continues to partner with the CDC to promote antibiotic stewardship through the *Get Smart* campaign. This year, activities will include an educational session at the 2015 Interim Meeting, with presenters from the CDC as well as the sharing of tools and guidelines through the AMA's communication vehicles.

CONCLUSION

Antibiotic resistance poses a serious threat to the health of the public. A coordinated, multi-sector, and multi-pronged approach is required to address the issue. Efforts need to be taken by both human and animal health sectors to promote adoption of antibiotic stewardship programs. Patients need to continue to be educated regarding the appropriate use of antibiotics. Incentives are needed to encourage the development of new antibiotics and infectious disease diagnostics. Public health and veterinary health systems need adequate funding for systematic surveillance of antibiotic use and resistance so there is a robust evidence-base for understanding the problem developing and implementing strategies for preventing the spread of human infections for which no effective treatment is available.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following recommendations be adopted and the remainder of the report be filed.

1. That the following new policy be adopted:

Surveillance of Antibiotic Use and Resistance
Our AMA: (1) recognizes the importance of public health and veterinary health surveillance for antimicrobial resistance and antibiotic use; and (2) recommends that public health and veterinary health agencies be adequately funded, as outlined in the President's Council of Advisors on Science and Technology Report, to achieve the surveillance goals and objectives outlined in the National Action Plan for Combating Antibiotic Resistant Bacteria. (New HOD Policy)

2. That policy H-100.952 be amended by addition and deletion to read as follows:

H-100.952 Enhancing Antibiotic Stewardship in the Human Health Care Setting to Improve Patient Outcomes ~~in the Inpatient Setting~~.
Our AMA will: (1) support antimicrobial stewardship programs, overseen by qualified physicians, as an effective way to ensure appropriate antibiotic use to reduce the burden of antimicrobial resistance, to ~~optimize~~ improve patient outcomes, and to reduce overall costs for ~~a~~ health care facilit~~y~~ies and systems. Antibiotic stewardship programs are systematic, multi-faceted, patient safety programs, and use evidence-based approaches to optimize antibiotic prescribing, encompassing components such as policy, guidelines, surveillance, education, epidemiology ~~of current resistance~~, ~~and~~ process, and outcome measurement. Successful antibiotic stewardship programs monitor and direct antimicrobial use, providing a standard, evidence-based approach to judicious antibiotic use ~~in a healthcare facility~~ across the spectrum of care, including, but not limited to acute care hospitals, outpatient clinics, emergency departments and long-term care facilities;
(2) support the development of antibiotic stewardship programs that allow flexibility so that adherence to national requirements does not limit the ability of providers to design programs based on local variables, such as health care facility size, patient population served, and care delivery setting (e.g., outpatient v. inpatient) and to address local antimicrobial stewardship and infection prevention challenges;
(3) urge each health care facility's governing body to promote and support robust, physician-led antimicrobial stewardship and infection prevention programs as critical components of assuring safe patient care; and
(4) support continued research into the impact of antibiotic stewardship programs on process outcomes and encourage increased research on the impact of such programs on patient-centered outcomes. (BOT Rep. 20, A-12)

3. That the following policies be reaffirmed:

H-100.953 Establishment of a Limited Population Antibacterial Drug Approval Pathway
H-100.960 The 10x 20 Initiative (10 New Antibiotics by 2020)
H-100.973 Combating Antimicrobial Resistance through Education
H-440.834 Next Generation Infectious Diseases Diagnostics
D-100.998 Combating Antibiotic Resistance Via Physician Action and Education: AMA Activities
H-440.846 Antibiotic Use in Food-Producing Animals

4. That the following directives be rescinded since they have been implemented:

D-100.995 Antimicrobial Use and Resistance
Our AMA will work with other organizations to establish a national program to counter antibiotic resistance in clinical practice similar to the California Medical Association Foundation AWARE program. (Res. 508, A-01; Reaffirmation I-07; Reaffirmation A-09)

D-440.991 Antimicrobial Use and Resistance
Our AMA will urge that increased surveillance of antimicrobial use and resistance be funded and instituted as recommended by the Institute of Medicine and American Society of Microbiology. (Res. 508, A-01; Reaffirmation A-09)

Fiscal Note: Less than $500

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APPENDIX A

Current AMA Policy

E-9.0652 Physician Stewardship of Health Care Resources
Physicians' primary ethical obligation is to promote the well-being of individual patients. Physicians also have a long-recognized obligation to patients in general to promote public health and access to care. This obligation requires physicians to be prudent stewards of the shared societal resources with which they are entrusted. Managing health care resources responsibly for the benefit of all patients is compatible with physicians' primary obligation to serve the interests of individual patients.
To fulfill their obligation to be prudent stewards of health care resources, physicians should: (a) Base recommendations and decisions on patients' medical needs; (b) Use scientifically grounded evidence to inform professional decisions when available; (c) Help patients articulate their health care goals and help patients and their families form realistic expectations about whether a particular intervention is likely to achieve those goals; (d) Endorse recommendations that offer reasonable likelihood of achieving the patient's health care goals; (e) Choose the course of action that requires fewer resources when alternative courses of action offer similar likelihood and degree of anticipated benefit compared to anticipated harm for the individual patient, but require different levels of resources; (f) Be transparent about alternatives, including disclosing when resource constraints play a role in decision making; and (g) Participate in efforts to resolve persistent disagreement about whether a costly intervention is worthwhile, which may include consulting other physicians, an ethics committee, or other appropriate resource. Physicians are in a unique position to affect health care spending. But individual physicians alone cannot and should not be expected to address the systemic challenges of wisely managing health care resources. Medicine as a profession must create conditions for practice that make it feasible for individual physicians to be prudent stewards by: (h) Encouraging health care administrators and organizations to make cost data transparent (including cost accounting methodologies) so that physicians can exercise well-informed stewardship; (i) Ensuring that physicians have the training they need to be informed about health care costs and how their decisions affect overall health care spending; and (j) Advocating for policy changes, such as medical liability reform, that promote professional judgment and address systemic barriers that impede responsible stewardship. (I, V, VII, VII, IX) Issued November 2012 based on the report "Physician Stewardship of Health Care Resources," adopted June 2012.

H-100.952 Enhancing Antibiotic Stewardship to Improve Patient Outcomes in the Inpatient Setting
1. Our AMA will: (1) support antimicrobial stewardship programs, overseen by qualified physicians, as an effective way to ensure appropriate antibiotic use, to optimize patient outcomes, and to reduce overall costs for a healthcare facility. Antibiotic stewardship programs are multi-faceted approaches to optimize antibiotic prescribing, encompassing components such as policy, guidelines, surveillance, education, epidemiology of current resistance, and process measurement. Successful antibiotic stewardship programs monitor and direct antimicrobial use, providing a standard, evidence-based approach to judicious antibiotic use in a healthcare facility; (2) support the development of antibiotic stewardship programs that allow flexibility so that adherence to national requirements does not limit the ability of providers to design programs based on local variables, such as healthcare facility size, and to address local antimicrobial stewardship and infection prevention challenges; (3) urge each healthcare facility's governing body to promote and support robust antimicrobial stewardship and infection prevention programs as critical components of assuring safe patient care; and (4) support continued research into the impact of antibiotic stewardship programs on process outcomes, and encourage increased research on the impact of such programs on patient-centered outcomes. (BOT Rep. 20, A-12)

H-100.953 Establishment of Limited Population Antibacterial Drug Approval Pathway
1. Our AMA supports establishment of the Limited Population Antibacterial Drug (LAPD) mechanism to provide a predictable and feasible Food and Drug Administration approval pathway for pharmaceutical companies seeking to develop antibacterial drugs to treat serious and life-threatening infections where there is a lack of sufficient or satisfactory therapeutic options through legislative or regulatory means. 2. Should the LPAD be established, our AMA shall work with the Infectious Diseases Society of America, other medical societies, and the health care community to educate providers about LPAD products, including their benefits and risks. (Res. 231, A-12)

H-100.954 Stimulate Antibiotic Research and Development
Our AMA supports legislation requiring the re-evaluation of FDA guidelines for clinical trials of antibiotics, including an increase in the period of market exclusivity. (Res. 210, A-12)

H-100.960 The 10 x ’20 Initiative (10 New Antibiotics by 2020)
Our AMA: (1) supports efforts to educate physicians, the Administration, Congress, and the public about the problem of antimicrobial resistance and the lack of new antibiotics in the drug development pipeline; and (2) endorses the 10 x ’20 Initiative (10 new antibiotics by 2020) and supports efforts to bring together experts from the industrial, medical, scientific, policy, regulatory, and financial communities to determine and adopt the right combination of incentives needed to create a sustainable antibiotic research and development enterprise. (Res. 505, A-10)

H-100.973 Combating Antimicrobial Resistance through Education
Our AMA: (1) encourages the federal government, the World Health Organization, the World Medical Association, and the International Federation of Pharmacists to promote more effective education concerning the appropriate use of antibiotics; (2) strongly urges physicians to educate their patients about their antimicrobial therapy, the importance of compliance with the prescribed regimen, and the problem of antimicrobial resistance; (3) will continue to educate physicians and physicians-in-training about the appropriate prescribing of antimicrobial agents; (4) encourages the use of antibiotic resistance management programs; these education-based programs should be multidisciplinary and cooperative (i.e., including infectious disease physicians, infection-control specialists, microbiology laboratory personnel, and clinical pharmacists); and (5) encourages continued scientific research on the issue of antibiotic resistance. (Sub. Res. 521, A-94; Reaffirmed by Rules & Credentials Cmt., A-96; Reaffirmation I-98; Modified: CSA Rep. 3, A-00; Reaffirmation I-07)

D-100.976 Restriction of Non-Veterinary Antimicrobials in Commercial Livestock to Reduce Antibiotic Resistance
Our AMA will work with interested partners to develop new, or improve existing, FDA guidelines concerning the prudent use of antibiotics in livestock to protect patients from the dangers of antimicrobial-resistant pathogens. (Res. 530, A-08)

D-100.995 Antimicrobial Use and Resistance
Our AMA will work with other organizations to establish a national program to counter antibiotic resistance in clinical practice similar to the California Medical Association Foundation AWARE program. (Res. 508, A-01; Reaffirmation I-07; Reaffirmation A-09)

D-100.997 Use of Antimicrobials in Consumer Products
Our AMA will: (1) encourage the Food and Drug Administration (FDA) to expedite their regulation of the use in consumer products of antimicrobials for which acquired resistance has been demonstrated; (2) monitor the progress of the current FDA evaluation of the safety and

effectiveness of antimicrobials for consumer use in over-the-counter (OTC) hand and body washes; and (3) encourage continued research on the use of common antimicrobials as ingredients in consumer products and its impact on the major public health problem of antimicrobial resistance. (CSA Rep. 2, A-00; Reaffirmed: CSAPH Rep. 1, A-10)

D-100.998 Combating Antibiotic Resistance Via Physician Action and Education: AMA Activities
Our AMA will continue to collaborate with the appropriate federal agencies, other medical specialty societies, and other appropriate public health organizations to address the urgent problem of increasing antimicrobial resistance and its impact on public health. (CMS Rep. 3, A-00; Reaffirmation I-07; Reaffirmation A-09)

H-440.846 Antibiotic Use in Food-Producing Animals
Our AMA supports: (1) federal efforts to ban antibiotic use in food-producing animals for growth promotion purposes, including through regulatory and legislative measures; (2) a strong federal requirement that antibiotic prescriptions for animals be overseen by a veterinarian knowledgeable of the place and intended use of these drugs, under a valid veterinarian-client-patient relationship (VCPR); and (3) efforts to expand FDA surveillance and data collection of antibiotic use in agriculture. (Res. 513, A-14)

H-440.856 Hospital Dress Codes for the Reduction of Health Care-Associated Infection Transmission of Disease
Our AMA encourages: (1) research in textile transmission of health care-associated infections (HAI); (2) testing and validation of research results before advocating for adoption of dress code policies that may not achieve reduction of HAIs; (3) all clinicians to assume “antimicrobial stewardship,” i.e., adherence to evidence-based solutions and best practices to reduce of HAIs and HAI infection rates; and (4) all clinicians when seeing patients to wear attire that is clean, unsoiled, and appropriate to the setting of care. (BOT Rep. 3, A-10)

D-440.938 Triclosan Antimicrobials
Our AMA will encourage the Food and Drug Administration to finalize the triclosan antimicrobial monograph first drafted in 1978 and updated in 1994 which found evidence for the safety and effectiveness of only alcohol and iodine-based topical products in health care use and will encourage the education of members on the issue of the importance of proper hand hygiene and the preferential use of plain soap and water or alcohol-based hand sanitizers in health care settings, consistent with the recommendations of the Centers for Disease Control and Prevention. (Res. 513, A-12)

D-440.991 Antimicrobial Use and Resistance
Our AMA will urge that increased surveillance of antimicrobial use and resistance be funded and instituted as recommended by the Institute of Medicine and American Society of Microbiology. (Res. 508, A-01; Reaffirmation A-09)

Res. 507 (A-15) Next Generation Infectious Disease Diagnostics
That our American Medical Association support: (1) strong federal efforts to stimulate early research and development of emerging rapid ID diagnostic technologies through increased funding for appropriate agencies; (2) the reduction of regulatory barriers to allow for safe and effective emerging rapid diagnostic tests, particularly those that address unmet medical needs, to more rapidly reach laboratories for use in patient care; (3) improving the clinical integration of new diagnostic technologies into patient care through outcomes research that demonstrates the impact of diagnostics on patient care and outcomes, educational programs and clinical practice guidelines for health care providers on the appropriate use of diagnostics, and integration of diagnostic tests

results into electronic medical records; (4) efforts to overcome reimbursement barriers to ensure coverage of the cost of emerging diagnostics. (New AMA Policy)

APPENDIX B

Choosing Wisely Recommendations

Specialty Society	Recommendation	Date
American Academy of Allergy, Asthma & Immunology	Don't order sinus computed tomography (CT) or indiscriminately prescribe antibiotics for uncomplicated acute rhinosinusitis.	April 4, 2012
	Don't overuse non-beta lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation	March 3, 2014
American Academy of Dermatology	Don't routinely use antibiotics to treat bilateral swelling and redness of the lower leg unless there is clear evidence of infection	August 19, 2015
	Don't routinely prescribe antibiotics for inflamed epidermal cysts	August 19, 2015
	Don't routinely use topical antibiotics on a surgical wound.	October 29, 2013
	Don't use oral antibiotics for treatment of atopic dermatitis unless there is clinical evidence of infection.	October 29, 2013
American Society for Metabolic and Bariatric Surgery	Avoid routine postoperative antibiotics.	June 25, 2015
American Academy of Family Physicians	Don't prescribe antibiotics for otitis media in children aged 2-12 years with non-severe symptoms where the observation option is reasonable.	September 24, 2013
	Don't routinely prescribe antibiotics for acute mild-to-moderate sinusitis unless symptoms last for seven or more days, or symptoms worsen after initial clinical improvement.	April 4, 2012
American Academy of Ophthalmology	Don't order antibiotics for adenoviral conjunctivitis (pink eye).	February 21, 2013
	Don't routinely provide antibiotics before or after intravitreal injections.	February 21, 2013
American Academy of Otolaryngology—Head & Neck Surgery Foundation	Don't routinely use perioperative antibiotics for elective tonsillectomy in children.	February 17, 2015
	Don't prescribe oral antibiotics for uncomplicated acute external otitis.	February 21, 2013
	Don't prescribe oral antibiotics for uncomplicated acute tympanostomy tube otorrhea.	February 21, 2013
American Academy of Pediatrics	Avoid routine continuation of antibiotic therapy beyond 48 hours for initially asymptomatic infants without evidence of bacterial infection.	July 20, 2015
	Antibiotics should not be used for apparent viral respiratory illnesses (sinusitis, pharyngitis, bronchitis)	February 21, 2013
American College of Emergency Physicians	Avoid prescribing antibiotics in the emergency department for uncomplicated sinusitis.	October 27, 2014
	Avoid antibiotics and wound cultures in emergency department patients with uncomplicated skin and soft tissue abscesses after successful incision and drainage and with adequate medical follow-up.	October 14, 2013

American Geriatrics Society	Don't use antimicrobials to treat bacteriuria in older adults unless specific urinary tract symptoms are present.	February 21, 2013
American Society of Plastic Surgeons	Avoid continuing prophylactic antibiotics for greater than 24 hours after a surgical procedure.	June 4, 2012
American Urological Association	Don't prescribe antimicrobials to patients using indwelling or intermittent catheterization of the bladder unless there are signs and symptoms of urinary tract infection.	June 11, 2015
	Don't treat an elevated PSA with antibiotics for patients not experiencing other symptoms.	February 21, 2013
American Urogynecologic Society	Avoid using a fluoroquinolone antibiotic for the first-line treatment of uncomplicated urinary tract infections (UTIs) in women.	May 5, 2015
Infectious Disease Society of America	Avoid prophylactic antibiotics for the treatment of mitral valve prolapse.	February 23, 2015
	Avoid prescribing antibiotics for upper respiratory infections.	February 23, 2015
	Don't treat asymptomatic bacteruria with antibiotics.	February 23, 2015
	Don't use antibiotic therapy for stasis dermatitis of lower extremities.	February 23, 2015

FIGURE 1