

REPORTS OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

The following reports, 1–3, were presented by Louis J. Kraus, MD, Chair:

1. NON-MEDICAL EXEMPTIONS TO IMMUNIZATION

Reference committee hearing: see report of [Reference Committee K](#).

**HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS
IN LIEU OF RESOLUTION 904
REMAINDER OF REPORT FILED**

See Policies H-440.830, H-440.831 and H-440.970

Policy D-440.936, “Immunization Exemptions,” directs our American Medical Association (AMA) to review and address existing inconsistencies in its policies regarding immunization exemptions. While current AMA policy allows for immunization exemption for medical contraindications, AMA policy is not uniform regarding non-medical exemptions. Some policies (excluding ethical opinions) recognize only non-medical exemptions based on religious beliefs, while others recognize non-medical exemptions based on both religious and philosophical objections (Appendix A).

In an attempt to implement Policy D-440.936, the Council on Science and Public Health (CSAPH) and Council on Ethical and Judicial Affairs (CEJA) submitted a joint report at A-15 that was referred by the House of Delegates (HOD). Several policies were adopted at A-15 in support of eliminating non-medical exemptions (Appendix A). This report updates the scientific literature on this topic and recommends consolidation and revisions to existing AMA policy on vaccines and immunizations, while maintaining strong support for the elimination of non-medical exemptions, in order to best protect public health.

BACKGROUND

Immunization benefits both the individuals who receive vaccines and the wider community. When people are immunized, they not only build up their own immune systems, they also help prevent the spread of disease to others who have not been immunized, for whom the vaccine has failed to provide protection, or for whom the vaccine is medically contraindicated. Herd immunity—high immunization rates that help minimize the transmission of disease through a population—protects unimmunized and under-immunized individuals and those who are at highest risk for severe infection, including pregnant women, infants, immunocompromised individuals, and patients with chronic disease.

Law and policy throughout the United States require immunizations or other documentation of immunity as a condition of public school attendance and, in some cases, as a condition of employment.¹ The U.S. Supreme Court has held that states can mandate immunizations to protect public health, but, if they do, they also must allow medical exemptions. Courts have further held that the exemption process must not violate individuals’ constitutional rights. Most states also provide for non-medical exemptions to accommodate the religious beliefs of some individuals who oppose immunization. Some states also have expanded non-medical exemptions for certain individuals who oppose immunization based on broader personal or philosophical reasons.

Many states also have laws providing for mandatory immunizations during a public health emergency or large-scale outbreak of a communicable disease.¹ Generally, the power to order such action resides with the governor of the state or with a state health officer. While exemptions may currently be permitted for medical, religious, or philosophical reasons, governments have the authority to quarantine unimmunized individuals during a public health emergency.

VACCINE MANDATES & EXEMPTIONS

Immunization programs in the United States, supported by state legal requirements and federal funding/oversight, are among the most cost-effective and widely used public health interventions, having controlled or eliminated the spread of epidemic diseases including smallpox, measles, mumps, rubella, diphtheria, and polio.^{2,3}

Medical exemptions from immunization are intended to prevent harm to individuals who are at increased risk of adverse events from the vaccine because of underlying conditions. Vaccines are medically contraindicated for individuals who have histories of severe allergic reactions from prior doses of vaccine. Many underlying conditions also place individuals at increased risk of complications from certain vaccines, as well as from the diseases they prevent. For example, individuals who are severely immunocompromised should not be inoculated with vaccines containing live attenuated viruses, such as the varicella zoster (chicken pox or shingles) or measles, mumps, and rubella (MMR) vaccines.⁴ Individuals for whom vaccines are medically contraindicated are protected from exposure to vaccine-preventable diseases through herd immunity, i.e., high rates of vaccination among the rest of the population that minimize transmission throughout the population.

Non-medical exemptions recognize the role of individual and, for childhood immunizations, parental autonomy, in making decisions about immunization.⁵ These exemptions are variously defined across the country, encompassing religious exemptions and exemptions for “personal belief,” which may include philosophical or other strongly held non-medical reasons for objecting to immunization that are not associated with specific religious beliefs.

Childcare & School Entry Mandates

Every state and the District of Columbia (DC) has laws requiring documentation of immunizations for entry into licensed childcare, Head Start, and school.⁶ Various states also mandate immunizations for incoming college and university students. The CDC maintains a continuously updated online database of state laws pertaining to immunization requirements for childcare, kindergarten, middle school, and university/college attendance.⁷ Institutions, such as colleges and private schools, may establish additional immunization policies for attendance or residence on campus. School entry coverage for most states is at or near national *Healthy People 2020* targets of maintaining 95% immunization coverage levels for all recommended vaccines.^{8,9}

Requirements for exemptions from childcare and school entry vaccine mandates vary from state to state with regard to the child’s age, school grades covered, the vaccines included, the processes and authority used to add or remove vaccines from school entry mandates, reasons for exemptions (medical reasons, religious reasons, philosophical or personal beliefs), and the procedures for granting exemptions.¹⁰⁻¹² All states allow exemptions when there is a medical contraindication such as immune deficiency or an allergic reaction.¹³ As of July 2015, 48 states allow a religious exemption (West Virginia and Mississippi are the only exceptions); 19 states also allow a “personal belief” exemption.¹⁴ In June 2015, the governor of California signed a bill that prohibits personal and religious belief exemptions. The law will go into effect on July 1, 2016.¹⁵

It has been observed in several studies that allowing non-medical exemptions is correlated with decreased vaccination coverage. Additionally, in states that allow philosophical exemptions, such exemptions often dominate the majority of all exemptions.¹⁶ For the 2013-2014 school year, an estimated 90,666 exemptions were reported nationally among a total estimated population of 3,902,571 kindergarten-age children.⁸ Exemption rates were less than 1% for eight states and greater than 4% for 11 states (range: less than 0.1% in Mississippi to 7.1% in Oregon; median 1.8%). During the 2014-2015 school year, approximately 94% of children attending kindergarten received two doses of measles, mumps, and rubella (MMR) vaccine, and met the local requirements for diphtheria, tetanus, and acellular pertussis (Dtap) vaccine. The median percentage of any exemptions was 1.7%, with pockets of low and high exemption rates by state.¹⁷ The recent measles outbreak that began with exposure at a California amusement park not only helped initiate the non-medical exemption legislation in California, but lawmakers in 7 additional states are currently considering measures to either eliminate or restrict vaccine exemptions or expand vaccine mandates as well.¹⁸

All states permit a medical exemption to immunization for children entering childcare and school. In states that report medical exemptions separately from non-medical exemptions, the median medical exemption rate for kindergarten-age children in the 2013-2014 school year was 0.2% (range: less than 0.1% in eight states to 1.2% in Alaska and Washington).⁸

Over the past two decades, the number of non-medical exemptions from school immunization requirements in the United States has increased considerably, from a state median of 0.98% in 1991 to 1.7% in 2014,^{8,10,19-24} primarily among states that recognize exemptions based on personal or philosophical beliefs in addition to religious exemptions. In states that report medical exemptions separately from non-medical exemption rates, for the 2013-

2014 school year, the median percentage of kindergarten-age children with non-medical exemptions was 1.7% (range: 0.4% in Virginia to 7.0% in Oregon); 11 states had non-medical exemptions levels of 4.0% or greater.⁸

Immunization of Health Care Personnel

The CDC recommends that all health care personnel be immunized appropriately.²⁵ A number of states require employees of certain health care facilities, such as hospitals and nursing homes, to be immunized against diseases such as measles, mumps, rubella, varicella zoster, hepatitis B, and influenza. Such laws, which vary widely, generally contain opt-out provisions for vaccines that are medically contraindicated or contrary to the individual's religious or philosophical beliefs.²⁶

As of July 2015, three states (Alabama, Colorado, and New Hampshire) mandated influenza immunizations for health care personnel.²⁷ Even without a state mandate, hospitals and health care systems in 45 states have implemented institutional policies mandating influenza immunization, although these policies vary in their requirements and penalties.²⁸ As of 2014, approximately 30% of health care personnel reported that their employers required influenza immunization as a condition of employment.²⁹ Evidence from the literature suggests that vaccine mandates among health care personnel are directly associated with increased vaccination rates.³⁰

For the 2013-2014 influenza season, 82% of health care personnel overall reported having had an influenza immunization,³¹ which is below the *Healthy People 2020* annual goal of 90% influenza vaccine coverage for this group.⁹ However, this rate varied considerably by state.³¹ Immunization coverage also varied according to occupation. For the 2013-2014 season, immunization coverage was 92% among physicians, 90.5% among nurses, 90% among nurse practitioners and physician assistants, 87% among other clinical personnel, and 69% among nonclinical personnel.²⁷ Immunization coverage was 90% among health care personnel working in hospitals and 63% among those working in long-term care facilities.²⁷

IMMUNIZATION STATUS & THE RESURGENCE OF VACCINE-PREVENTABLE DISEASES

A growing number of parents are seeking non-medical exemptions to delay or refuse some or all vaccines for their children.^{27-29, 32-34} The ease of obtaining non-medical exemptions is associated with higher rates of exemptions,^{12,23,35} and there is reason to believe that parents may use non-medical exemptions out of convenience rather than deeply held belief.^{12,23,35} A study of non-medical exemptions permitted between 1991 to 2004 found that the increase in exemption rates was not uniform.²³ Exemption rates for states that allowed only religious exemptions remained at approximately 1% during this time period; however, in states that allowed exemptions for philosophical or personal beliefs, the mean exemption rate increased from 1% to 2.5%. Additional studies suggest that states that allow philosophical exemptions for school-age children have significantly higher rates of unimmunized children.^{8,10,21-24,35,36}

Overall, about 90% of all non-medical exemptions for states that permit both religious and philosophical exemptions for school entry were philosophical exemptions.⁸ Some states require membership in a recognized religion in order for a parent to invoke a religious exemption to vaccination of a student, whereas others merely require an affirmation of religious or philosophical opposition. States in which individuals can obtain vaccine exemptions for non-religious philosophical reasons generally have the highest immunization opt-out rates in the nation.^{8,24,36} Washington State, for example, has seen decreases in immunization rates among kindergartners. In particular, the percentage of kindergartners vaccinated against polio has dropped from 95.4% in 1998 to 88.4% in 2015,³⁷ well below the *Healthy People 2020* goal of 95%.⁹ Moreover, in 2015, the polio immunization rate among kindergartners in Seattle was even lower than the state average, at 81.4%. According to the World Health Organization (WHO), this rate is lower than polio immunization rates in countries such as Algeria, El Salvador, Guyana, Iran, Kyrgyzstan, Mongolia, Rwanda, Sudan, Yemen, and Zimbabwe, among others.³⁷

Where immunization rates are low, especially where children are under-immunized or not immunized at all, outbreaks of vaccine-preventable disease are more frequent.³⁸⁻⁴³ Studies have shown an increase in the local risk of vaccine-preventable diseases (notably pertussis, measles, and mumps) when individuals who refuse immunization cluster geographically within school districts, communities, and counties.^{23,24,41-48} In Colorado, for example, the county-level incidence of measles in immunized children from 1987 through 1998 was associated with the frequency of exemptions in that county.⁴¹ Vaccine-exempt children were 22 times more likely to acquire measles and 6 times more likely to acquire pertussis than immunized children. At least 11% of vaccinated children who

acquired measles were infected through contact with an exempt child. The mean exemption rate among schools with pertussis outbreaks was 4.3% compared with 1.5% for schools that did not have an outbreak.

From January 1, 2014 to August 21, 2015, the United States has experienced a dramatic increase in the number of measles cases. During this time, the CDC confirmed 856 measles cases. In 2014, there were 668 cases in 27 states stemming from 23 outbreaks. Many of these outbreaks began with unimmunized individuals who were exposed to the virus while abroad, particularly those who travelled to the Philippines, which experienced a large measles outbreak. One large outbreak included 383 cases in unimmunized Amish communities in Ohio. As of August 2015, 188 cases of measles have been confirmed in 24 states and the District of Columbia. These cases have grown out of 5 major outbreaks,⁴⁹ with 125 cases from a large multi-state outbreak linked to transmission at an amusement park in California, of which 55% of cases were unimmunized. The majority of cases (88%) were residents of California; of those individuals who were unvaccinated but eligible for vaccination, 37 (76%) were unvaccinated due to personal beliefs.⁵⁰ In addition, the majority of the cases that have occurred in the U.S. thus far have been among persons who were unimmunized.^{49,51}

VACCINE REFUSAL

While the vast majority of parents in the United States have their children immunized in accordance with the [Advisory Committee on Immunization Practices](#) (ACIP)-recommended vaccine schedule, it has been estimated that almost 1 in 8 parents (12%) have refused at least one vaccine recommended by their child's physician.⁵² Studies indicate that under-immunized children are likely to have missed some immunizations because of factors related to the health care system or socioeconomic characteristics, whereas children who are not immunized at all are likely to belong to families that intentionally refuse vaccines.¹⁰

Decisions about immunization are influenced by the individual's perception of health, beliefs about and experience of childhood diseases, and perceptions about the risks of diseases, as well as perceptions about vaccine safety and effectiveness, vaccine components, and level of trust in institutions.⁵³⁻⁶¹ Even when they do not reject immunization outright, many parents have become "vaccine hesitant."^{62,63} Having had little or no experience with most of the vaccine-preventable diseases because the prevalence of those diseases is very low (or nonexistent), parents' concerns that a vaccine will adversely affect their child can often outweigh their concerns about disease risk. Additionally, lack of understanding about how vaccines work combined with the fear of being injected with a disease agent contribute to reluctance to undergo immunization. In past surveys, parents consistently cited vaccine safety, including concerns about autism, as the most frequent reason for not vaccinating their children.^{10,53-55,59,60,64} More recently, the primary reasons for parents' failure to vaccinate their children include issues related to lack of perceived need of vaccination, vaccine safety, lack of trust in the government or their health care provider, and perceived lack of involvement in the decision-making process for their children. In addition, the perceived link between vaccines and autism still remains a large concern of parents seeking exemptions for immunization.⁶⁵ The evidence that originally purported to show a link between autism and immunization was proven to be fraudulent and was retracted and its author censured.⁶⁶ An extensive body of credible scientific evidence continues to support the safety and effectiveness of vaccines.⁶⁷⁻⁷⁰

Parents who refuse immunization for their children may also rely more on guidance from family, friends, and their broader social network, including popular media, than on physicians' recommendations.⁷¹ The influence of such social guidance is evident in the persistence of the anti-immunization movement in the United States,⁷² and the geographical clustering of families with similar attitudes and beliefs about immunizations.^{23,24,41-48}

A majority of states do not specifically define what constitutes a religious or personal exemption; when they do, how strictly the exemption is defined does not appear to determine how strictly the exemption is applied.²⁷ In some states, a parent can claim personal exemption simply by signing a prewritten statement on the school immunization form.²⁵ Often this is perceived as easier than completing a school immunization form that requires a health care professional to provide details of immunization from the child's medical record. Some states that offer religious or personal belief exemptions have additional administrative requirements, such as requiring a signature from a local health department official, annual renewal, notarization, or a personally written letter from the parents explaining the reasons for vaccine refusal. Research supports a relationship between rates of non-medical exemptions and the process in place for obtaining them: the easier the process, the higher the rate of exemptions.³⁵ Moreover, exemption rates are higher in states that permit non-medical exemptions for personal and philosophical, rather than solely religious, reasons.³⁵

In light of recent measles outbreaks,⁴⁹ views regarding non-medical exemptions appear to be shifting among parents in the U.S. A 2015 national poll on children's health, conducted by the University of Michigan C.S. Mott Children's Hospital, asked parents if their views about vaccination had changed since the prior year. Compared to their views a year ago, 25% of parents surveyed believed vaccination to be safer, 34% thought vaccines are more beneficial, and 35% are more supportive of vaccine requirements for schools and daycare facilities.⁷³

PHYSICIAN ROLE IN IMMUNIZATION

Physicians can play an important role in engaging and supporting vaccine-hesitant parents to understand and address their concerns. Physicians have long-recognized obligations to promote health and prevent disease for the well-being of individual patients and the community at large.⁷⁴ Physicians likewise have an obligation not to put patients at undue risk of harm. As trusted sources of information and guidance, physicians can play a significant role in shaping their patients' perspectives about vaccines and the decisions patients make about immunizing themselves and their families.^{21, 53-58} Physicians have a responsibility to educate parents/guardians about the long-term preventive benefits of childhood immunizations.

Physicians' responsibility to protect patients' well-being extends to ensuring that they and all staff in their own practices are immunized, absent medical contraindication. Parents/guardians of minor patients who continue to refuse immunization for their children, as well as adult patients who refuse immunization for themselves, pose a health risk to others. Because physicians have an obligation to protect the health of the other patients in the practice and the practice staff, physicians must take action to protect those who will come in contact with unimmunized individuals in the office, clinic, or other health care setting.

CONCLUSION

The reemergence of various vaccine-preventable diseases argues for the removal of non-medical exemptions to immunization mandates. Where exemption rates are high, herd immunity may be compromised and the number of unimmunized individuals might become sufficient to permit transmission of vaccine-preventable diseases, if introduced. When people decide not to be immunized, they put others at risk as well as themselves. Protecting community health requires that individuals not be permitted to opt out of immunization solely as a matter of convenience or misinformation. To protect public health and limit the resurgence of vaccine preventable diseases, all children and adults, including physicians and health professionals, should be immunized according to the recommended [Advisory Committee on Immunization Practices](#) (ACIP) schedule, unless medically contraindicated. Two states already prohibit non-medical exemptions to mandatory vaccination; another recently adopted legislation to do the same. This is wise public health policy and is the policy that should be adopted in all U.S. jurisdictions.

Physicians have an important role to play in protecting individual patients and the health of communities. They have a responsibility to help educate patients and parents about the risks of vaccine-preventable diseases and the safety and effectiveness of vaccines. Physicians who administer vaccines also need to stay up-to-date on the recommendations of the Advisory Committee on Immunization Practices for themselves and their patients.

RECOMMENDATIONS

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

1. That Policy H-440.970, Religious Exemptions from Immunizations, be amended by substitution to read as follows:

Nonmedical Exemptions from Immunizations

Our American Medical Association (AMA) believes that nonmedical (religious, philosophic, or personal belief) exemptions from immunizations endanger the health of the unvaccinated individual and the health of those in his or her group and the community at large. Therefore, our AMA (1) supports the immunization recommendations of the Advisory Committee on Immunization Practices (ACIP) for all individuals without medical contraindications; (2) supports legislation eliminating nonmedical exemptions from immunization; (3) encourages state medical associations to seek removal of nonmedical exemptions in statutes requiring mandatory immunizations, including for childcare and school attendance; (4) encourages physicians to grant

vaccine exemption requests only when medical contraindications are present; (5) encourages state and local medical associations to work with public health officials to develop contingency plans for controlling outbreaks in medically-exempt populations and to intensify efforts to achieve high immunization rates in communities where nonmedical exemptions are common; and (6) recommends that states have in place: (a) an established mechanism, which includes the involvement of qualified public health physicians, of determining which vaccines will be mandatory for admission to school and other identified public venues (based upon the recommendations of the ACIP); and (b) policies that permit immunization exemptions for medical reasons only.

2. That Policy H-440.831, Protecting Patients and the Public by Immunizing Physicians, be amended by substitution to read as follows:

Protecting Patients and the Public through Physician, Health Care Worker, and Caregiver Immunization

1. American Medical Association (AMA) policy is that, in the context of a highly transmissible disease that poses significant medical risk for vulnerable patients or colleagues or threatens the availability of the health care workforce, particularly a disease that has the potential to become epidemic or pandemic, including influenza, and for which there is an available, safe, and effective vaccine, physicians, health care workers (HCWs), and family caregivers who have direct patient care responsibilities or potential direct exposure have an obligation to accept immunization unless there is a recognized medical reason to not be immunized. In scenarios in which there is a documented medical contraindication to immunization of a physician or HCW, appropriate protective measures should be taken. 2. Our AMA (a) encourages hospitals, health care systems, and health care providers to provide immunizations to HCWs against influenza and other highly transmissible diseases, at no cost to the employee, both for their own protection and to reduce the risk of infectious disease transmission to others; and (b) encourages health care institutions to develop mechanisms to maximize the rate of influenza immunization for HCWs, including the option of making immunization a condition of employment.

3. That Policy H-440.830, Parent to Parent Education on Child Vaccination, be amended by substitution to read as follows:

Education on Vaccine Safety and Efficacy

Our American Medical Association (1) encourages the development and dissemination of evidence-based public awareness campaigns aimed at increasing vaccination rates; (2) encourages the development of educational materials that can be distributed to patients and their families clearly articulating the benefits of immunizations and highlighting the exemplary safety record of vaccines; (3) supports the development and evaluation, in collaboration with health care providers, of evidence-based educational resources to assist parents in educating and encouraging other parents who may be reluctant to vaccinate their children; (4) encourages physicians and state and local medical associations to work with public health officials to inform those who object to immunizations about the benefits of vaccinations and the risks to their own health and that of the general public if they refuse to accept them; (5) will promote the safety and efficacy of vaccines while rejecting claims that have no foundation in science; and (6) will continue its ongoing efforts with other immunization advocacy organizations to assist physicians and other health care professionals in effectively communicating to patients, parents, policy makers, and the media that vaccines do not cause autism and that decreasing immunization rates have resulted in a resurgence of vaccine-preventable diseases and deaths.

4. That Policies H-440.850, Recommendations for Healthcare Worker and Patient Influenza Immunizations; D-440.936, Immunization Exemptions; D-440.947, Support for Immunizations; H-440.829, Ending Non-Medical Exemptions for Immunization; H-440.832, Vaccination Requirements to Protect All Children; and H-440.853, Increasing Public Awareness of the Lack of a Vaccine-Autism Link be rescinded since they have been implemented or accomplished (in the case of D-440.936 and H-440.853), or have been rendered duplicative by the recommendations in this report (in the case of D-440.850, D-440.947, and H-440.829).

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APPENDIX - Current Vaccine Exemption Policies

H-440.832 Vaccination Requirements to Protect All Children

1. Our American Medical Association supports the dissemination of materials on vaccine efficacy to states, and encourages them to eliminate philosophical and religious exemptions from state immunization requirements. 2. Our AMA recommends that states have in place: (a) an established decision mechanism that involves qualified public health physicians to determine which vaccines will be mandatory for admission to school and other identified public venues (based upon the recommendations of ACIP and AAP); and (b) exemptions to these immunization mandates only for medical reasons, because disease exposures, importations, infections, and outbreaks may occur without warning in any community.

H-440.831 Protecting Patients and the Public by Immunizing Physicians

American Medical Association policy is that in the context of a highly transmissible disease that poses significant medical risk for vulnerable patients or colleagues, or threatens the availability of the health care workforce, particularly a disease that has potential to become epidemic or pandemic, and for which there is an available, safe, and effective vaccine, physicians and health care workers who have direct patient care responsibilities or potential direct exposure have an obligation to accept immunization unless there is a recognized medical reason to not be immunized. In such scenarios, appropriate protective measures should be taken.

H-440.830 Parent to Parent Education on Child Vaccination

In order to increase child vaccination rates, our American Medical Association supports the development and evaluation of educational efforts, based on scientific evidence and in collaboration with health care providers, that support parents who want to help educate and encourage parents reluctant to vaccinate their children.

H-440.829 Ending Non-Medical Exemptions for Immunization

1. Our American Medical Association supports legislation eliminating non-medical exemptions from immunization for participation in federally funded educational programs for children including Head Start. 2. Our AMA supports state medical society efforts to eliminate non-medical exemptions from immunization for childcare and school attendance in state statutes.

D-440.931 Encourage Autism Society to Support Vaccinations

Our American Medical Association will work jointly with the American College of Physicians, American Academy of Pediatrics and American Academy of Family Physicians to encourage the Autism Society of America to display on its website that based on current scientific evidence, autism is not caused by vaccinations, and encourage vaccinations to promote better health for all our population.

H-440.970 Religious Exemptions from Immunizations

Since religious/philosophic exemptions from immunizations endanger not only the health of the unvaccinated individual, but also the health of those in his or her group and the community at large, the AMA (1) encourages state medical associations to seek removal of such exemptions in statutes requiring mandatory immunizations; (2) encourages physicians and state and local medical associations to work with public health officials to inform religious groups and others who object to immunizations of the benefits of vaccinations and the risk to their own health and that of the general public if they refuse to accept them; and (3) encourages state and local medical associations to work with public health officials to develop contingency plans for controlling

outbreaks in exempt populations and to intensify efforts to achieve high immunization rates in communities where groups having religious exemptions from immunizations reside.

H-440.850 Recommendations for Healthcare Worker and Patient Influenza Immunizations

1. Our AMA (A) reaffirms its support for universal influenza vaccination of health care workers (HCWs) and supports universal immunization of HCWs against seasonal and pandemic influenza through vaccination programs undertaken by health care institutions in conjunction with medical staff leadership; (B) encourages all hospitals, health care systems, and health care providers to immunize providers and appropriate patients as defined by the Advisory Committee on Immunization Practices guidelines against both influenza and pertussis, as a priority, both for their own protection and to reduce the risk of transmission to others; and (C) will work to ensure that hospitals and skilled nursing facilities have a system for measuring and maximizing the rate of influenza immunization for health care workers. 2. Our AMA: (A) supports a mandatory annual influenza vaccination for every long term care health care worker who has direct patient contact unless a medical contraindication or religious objection exists; (B) recommends that medical directors and other practitioners encourage caregivers (both professional health care workers and family caregivers) to obtain these vaccinations; and (C) recommends vaccinations be made available and offered at no cost to staff working in long-term care settings.

D-440.947 Support for Immunizations

1. Our AMA will provide materials on vaccine safety and efficacy to states and encourage them to enact more stringent requirements for parents/legal guardians to obtain personal belief exemptions from state immunization requirements. 2. Our AMA, in collaboration with the Immunization Alliance, will develop educational materials that can be distributed to patients and their families clearly articulating the benefits of immunizations and highlighting the exemplary safety record of vaccines. 3. Our AMA will communicate and work with other concerned organizations about effective ways to continue to support immunizations while rejecting claims that have no foundation in science. 4. Our AMA will continue its ongoing efforts with other immunization advocacy organizations to assist physicians and other health care professionals to effectively communicate to patients, parents, policy makers, and the media that vaccines do not cause autism and that decreasing immunization rates have resulted in a resurgence of vaccine-preventable diseases and deaths; and will continue to support ongoing research into the etiology and treatment of autism. 5. Our AMA will actively oppose any vaccine legislation that would deviate from evidence-based recommendations and guidelines of the Centers for Disease Control and Prevention, the Advisory Committee on Immunization Practices, the American Academy of Family Physicians, the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists. 6. Our AMA encourages physicians to follow medical contraindications to vaccines when parents seek a note for a medical exemption from vaccines to attend school.

D-440.936 Immunization Exemptions

Our AMA will review and address existing inconsistencies in its policies regarding immunization exemptions

H-440.853 Increasing Public Awareness of the Lack of a Vaccine-Autism Link

Our AMA will ask the Office of the Surgeon General to offer a definitive repudiation of the link between either thimerosal-containing vaccines or the MMR vaccine and developmental disorders, such as autism.

2. NATIONAL DRUG SHORTAGES: UPDATE

Reference committee hearing: see report of [Reference Committee K](#).

**HOUSE ACTION: RECOMMENDATIONS ADOPTED
REMAINDER OF REPORT FILED**
See Policy H-100.956

INTRODUCTION

Policy H-100.956, “National Drug Shortages,” directs the Council on Science and Public Health (CSAPH) to continue to evaluate the drug shortage issue and report back at least annually to the House of Delegates (HOD) on progress made in addressing drug shortages in the U.S. This report provides an update on continuing trends in national drug shortages and ongoing efforts to further evaluate and address this critical public health issue and recommends amending current AMA policy. Several amendments are based on the fact that some previous sections of policy have been implemented or accomplished.

METHODS

English-language reports were selected from a PubMed and Google Scholar search from March 2014 to August 2015, using the text term “drug shortages” combined with “impact,” “crisis,” “oncology,” “chemotherapy,”

“antibacterial,” “pediatric(s),” “nutrition,” and “parenteral.” Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the U.S. Food and Drug Administration (FDA), American Society of Health-System Pharmacists (ASHP), PEW Charitable Trusts, Generic Pharmaceutical Association, International Society for Pharmaceutical Engineering (ISPE) the Pharmaceutical and Research Manufacturers of America, and by direct contact with key FDA and ASHP staff who manage drug shortage issues on a daily basis.

BACKGROUND

The Council has issued five previous reports on drug shortages.¹⁻⁵ The primary findings and conclusion from these reports can be summarized as follows:

- AMA activities to address the drug shortage issue started nearly 15 years ago with the convening of a special meeting of key FDA officials and representatives of the pharmaceutical industry, drug distributors, group purchasing organizations, the American Hospital Association, the Institute of Medicine, and the Department of Veteran Affairs (see CSAPH Report 2-I-11).
- Two primary sites have evolved that monitor and provide information on drug shortages--one maintained by the FDA and one maintained by ASHP. They differ in their criteria for inclusion of drug shortage information (see below).
- The FDA (federal government) cannot force or require any pharmaceutical manufacturer to produce a specific drug product.
- Although drug shortages have existed since 2000, the number and extent of drug shortages began worsening appreciably around 2007 and continued to worsen through 2011-2012, but recently signs of overall improvement are evident (see below). The most common drug shortage involves a generic sterile injectable product. Class-wide shortages in the sterile injectable drug industry are largely explained by an expansion in the scope and volume of products available for production without a corresponding increase in manufacturing capacity or redundancy.
- Quality problems are linked with a majority of sterile injectable shortages, in part, because production line processes for sterile injectables are complex. Generic companies operate a limited number of facilities, each containing multiple production lines, a portion of which are in need of upgrades. Cytotoxic drugs and certain antibiotics require specific equipment and regulatory approvals for their production lines. These special containment controls limit manufacturers’ ability to transfer production of these types of drugs to other lines (see CSAPH Report 7-A-12).
- Many causes of drug shortages exist, virtually all of which are remote from AMA influence. These include:
 - industry consolidation reducing the number of pharmaceutical manufacturers, in particular, companies manufacturing sterile injectable drug products. Consolidation also has resulted in fewer suppliers and the migration of manufacturing facilities to foreign sites;
 - corporate decisions leading to product discontinuation or decreased production in the free marketplace;
 - manufacturing difficulties and regulatory compliance issues; and
 - raw bulk material or active pharmaceutical ingredient shortages.
- Drug shortages have contributed to:
 - lack of treatment options and increased patient morbidity and mortality;
 - patient safety issues;
 - delays and cancellations in procedures;
 - the use of less efficacious and more expensive substitute treatments;
 - increased reliance on some compounded medications;
 - increased hospital costs and resource utilization; and
 - rationing of drugs in short supply.

- Multi-stakeholder meetings have been held to discuss potential solutions to the drug shortage problem considering regulatory and legislative factors, raw materials sourcing and manufacturing, business, market, and distribution factors (see CSAPH Reports 2-I-11 and 7-A-12).
- Reviews and comprehensive analyses of drug shortages have been released by the Office of Science and Data Policy (HHS), FDA, Government Accountability Office (GAO), and the IMS Institute for Healthcare Informatics. These reports have examined demand, supply, purchasing/pricing, and supplies and volume of sales over time. The GAO report identified multiple underlying causes of drug shortages, all of which were related to the economics of the generic sterile injectable market. Although the GAO attempted to probe stakeholders' views on the economic drivers of drug shortages, no consensus existed (see CSAPH Reports 2-A-12 and 3-A-14).
- Purchasing and pricing practices have come under increased scrutiny. Most sterile injectable drugs are purchased by hospitals (and in some cases physicians) through group purchasing organizations (GPOs), which negotiate prices with manufacturers. Drug delivery is accomplished by wholesalers who purchase inventory at the wholesale acquisition price with manufacturers issuing a "chargeback" if the acquisition price exceeds the GPO's negotiated price. GPO contracts typically have price adjustment clauses as well as "failure to supply" penalties. The latter usually do not apply when the product is not available. Pricing flexibility by suppliers may be constrained by long-term purchase contracts.
- Legislative and regulatory changes have increased the reporting responsibilities of drug manufacturers when a temporary or permanent disruption in drug supply is expected and required the FDA to develop a strategic plan to address drug shortages. In addition, the agency gained new responsibilities and tools for tracking drug shortages and attempting to mitigate them, including the use of expedited reviews (see CSAPH Reports 2-I-12 and 8-A-13).

Readers are referred to previous Council reports for further specific information on these and other topics.¹⁻⁵ While the attention of U.S. physicians has been focused on domestic supply problems, it is important to note that drug shortages are increasingly impacting health care on a global basis.^{6,7} The remainder of this report will update current trends and findings on drug shortages since the last Council report was developed in 2014 (CSAPH Report 5-A-14).

CURRENT TRENDS IN DRUG SHORTAGES

The two main data sources for information about trends in drug shortages in the United States continue to be the Drug Shortage Resource Center maintained by ASHP in cooperation with the University of Utah Drug Information Service and the Drug Shortage Program at the FDA. For a reminder on how the ASHP and FDA information and statistics on drug shortages are developed, see Table 1. Because their criteria differ (the main distinction being the FDA's definition of a "medically necessary drug"), the ASHP site lists more drug shortages than the FDA site. Physicians can directly report a drug shortage via the ASHP drug shortage website. The FDA also has developed apps for both the iPhone and Android operating systems that provide access to drug shortage information as well as notifications about new and resolved drug shortages.

American Society of Health-System Pharmacists

The ASHP's Drug Shortage Resource Center has been redesigned somewhat, containing categories reflecting current shortages, specific commercial preparations that are not currently available, drugs that are not being manufactured at all and are no longer available, resolved shortages, and as previously featured, guidelines and resources for managing shortages, as well as a mechanism to report a shortage.⁸

As of June 30, 2015, ASHP's Drug Shortage Resource Center identified 219 drugs in shortage, down from 310 at the end of the 3rd quarter in 2014. This number was further decreased to 180 drug shortages as of July 31, 2015; an additional 19 products were not commercially available.⁸ Fifty-eight manufactured drugs have been discontinued since 2010. The top active shortages by drug class are central nervous system agents, electrolytes and nutritional components, antimicrobials, cardiovascular drugs, and chemotherapeutic agents.

Food and Drug Administration

In June 2014, the FDA launched a drug shortage website to feature current/resolved shortages, discontinuations, the option of sorting by therapeutic category, and other resource information.⁹ As of July 31, 2015, the FDA reported that 67 drugs were currently in shortage (compared with 73 as of September 14, 2014), and 29 had been resolved. The latter are closely monitored because they may be at risk for falling back into shortage. The number of ongoing or active shortages has decreased by about 30% since 2013 (personal communication, Valerie Jensen, FDA).

Based on the passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012, companies are required to notify FDA of a permanent discontinuance or an interruption in manufacturing of certain drug products six months in advance, or if that is not possible, as soon as practicable. The shortage notification requirement has apparently reduced the number of new shortages by allowing FDA additional time to work with manufacturers to prevent shortages. The FDA's drug shortages website lists drugs that meet these criteria, reflecting shortage information supplied by manufacturers.¹⁰ A Final Rule published on July 27, 2015 provides further guidance on the notification process and adds biologic products to the requirements for notification about potential supply disruptions.¹¹

Drug Shortage Data System. In response to the GAO report on drug shortages, the FDA implemented a new system for data tracking to help ensure that "data are accurate and complete for analysis." The new system also centralizes various databases currently used by staff to assess the potential impact of shortages.¹² This database is not yet fully integrated with other data systems within the Center for Drug Evaluation and Research (CDER) and cannot be used at this time to reliably predict whether a manufacturer or product is at risk for shortage.

Drug Shortages Metrics Reported by FDA. The FDA's second annual report on drug shortages for calendar year 2014 (required by FDASIA) noted the following metrics during the first three quarters of calendar year 2014:¹²

- FDA was notified of 125 potential shortage situations by 52 different manufacturers.
- 78 new drug shortages were prevented.^a
- 100 generic abbreviated new drug or supplemental applications had expedited review.
- 10 inspections were prioritized to address a drug shortage.
- 5 fewer new drug shortages occurred in the first three quarters of 2014 (33) compared with the same period in 2013 (38).^b
- FDA exercised regulatory flexibility and discretion in 30 instances affecting 31 medically necessary products. Most of these involved measures to mitigate risks such as removing particulate matter, extra testing for quality, third-party oversight of production, provision of special instructions to prescribers and/or patients, or approval of foreign sources. With respect to the latter mitigation strategy, the FDA now conducts regular virtual meetings with their international regulatory counterparts to share information on drug shortages and mitigation strategies impacting patients in other countries.

An infographic developed by the FDA summarizes some of the recent pertinent findings and activities related to drug shortages.^c The most common reasons for drug shortages are quality/manufacturing issues (37%), manufacturing delays related to capacity (27%), raw materials (27%), increased demand (5%), loss of manufacturing site (2%), and product discontinuation (2%).

Shortages of Controlled Substances

In September 2014, CDER revised its Manual of Policies and Procedures, or MaPP, to clarify FDA's process for addressing shortages of controlled substances. The revised MaPP provides a framework for facilitating interaction between the FDA and DEA to mitigate drug shortages of controlled substances, as the DEA establishes annual production quotas for the manufacture of controlled substances. When FDA staff determines that a potential or actual shortage of a controlled substance may involve a request by the manufacturer to adjust production quotas (either for an active pharmaceutical ingredient or final dosage form of a Schedule II controlled substance), the FDA determines whether the DEA has been notified of a request to increase production. The FDA further requests clarification from the manufacturer on when they officially submitted their quota request to DEA, the outcome of

^aThe final total of new drug shortages prevented during 2014 was 101.

^bThe number of new drug shortages remained constant in 2013 and 2014 at 44, down from 117 in 2012.

^c<http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM441583.pdf>.

that request, and other information on the expected shortage. FDA then may work with DEA to enable a manufacturer to increase its allotted quota if this step would help avoid a shortage of the product.

CLINICAL IMPLICATIONS

Despite some success in preventing or mitigating drug shortages and an overall decrease in the number of new drug shortages, critical and perplexing shortages continue to occur, including sterile normal saline.

Shortages of Normal Saline

Although three large-volume infusion manufacturers exist in the U.S. and a fourth supplies dialysis centers, the demand for saline is very high. To meet demand and sell saline at a reasonable price, all four firms generally run production at peak capacity. Accordingly, in some cases a facility's capacity to ensure quality can be exceeded. For example, particulates, including hair fibers, appeared in one firm's saline, and in late 2013, all four firms simultaneously had quality issues that compromised production during the same period. Two of these issues precipitated recalls. Another manufacturer had a planned shutdown for routine maintenance, greatly reducing overall production capacity. The company that solely manufactures saline used in U.S. dialysis centers experienced import delays at its facility and temporarily could not supply its customers, forcing them to search for product elsewhere. For reasons that are not entirely clear, there also was a spike in saline demand at the end of 2013, which has not abated. The FDA worked with two of the four domestic saline manufacturers and one foreign firm that agreed to import saline from Spain, Norway, and Germany for U.S. use. The foreign firm is evaluating whether to join the U.S. market. Other firms are in the process of correcting their issues and adding capacity. See the FDA webpage on IV fluid shortages for further information on these workarounds based on foreign supply.^d

Recent case reports and analyses have continued to detail clinical consequences of drug shortages involving parenteral nutrition, emergency medicine, cardiovascular diseases/conditions, and oncology. As these shortages persist, cross-institutional collaboration efforts have been extended and institutional level guidelines for patient selection and management, including ethical constructs, have emerged.¹³⁻²⁰ Information about the clinical impact of drug shortages has largely been limited to broad-based surveys and case studies or case series in local and/or regional practice sites.

SOLUTIONS

A survey conducted by the International Society for Pharmaceutical Engineering (ISPE) regarding specific drug shortage issues that can lead to supply interruptions confirmed that problems were typically related to *quality* (or oversight that ensures compliance with current good manufacturing practices and quality control), *production* (activities and metrics that ensure performance of approved manufacturing procedures), and *facilities/equipment* (maintaining appropriate resources and physical environment for drug production).²¹ Production equipment used for aseptic production and particulate matter in end stage products continue to cause ongoing problems.²² An important barrier to facility maintenance or modernization is the length of time it takes, including the necessary regulatory approvals, to implement equipment upgrades.²² In developing a plan to prevent drug shortages, ISPE identified several key but interrelated categories for action, including developing a corporate culture that supports and advances quality, the need for a robust quality system and quality metrics, business continuity planning and capacity, transparent communication with authorities, and building sustained organizational capabilities to support these goals.²³

With respect to quality metrics, the FDA issued draft guidance on July 27, 2015 in an effort to begin collecting quality data to help assess facilities and their production processes with the intention to prioritize inspections based on the risk for quality problems. This approach is based on the premise that focusing on facilities that are at highest risk for quality problems will help mitigate drug shortages, given the fact that shortages are often the result of manufacturing issues.²⁴ FDA has expanded staffing in its drug shortage center and continues to explore long term strategies to prevent shortages as outlined in its 2013 strategic plan for preventing and mitigating drug shortages.²⁵

A Drug Shortages Summit was held on August 1, 2014 in Washington DC. The purpose of this summit was to examine in-depth the manufacturing, economic, and regulatory factors that contribute to drug shortages and consider

^d <http://www.fda.gov/Drugs/DrugSafety/ucm382255.htm>.

possible solutions. Organizers included the American Hospital Association, American Society of Anesthesiologists, American Society of Clinical Oncology, ASHP, the Institute for Safe Medication Practices, and the PEW Charitable Trusts. The AMA was one of several stakeholders from the public and private sector that participated. Broad issues addressed by the summit included potential manufacturing, production capacity and regulatory contributors to drug shortages; economic factors in drug shortages, including “health” of the marketplace; assessing the need for incentives (e.g., tax incentives, government support of the market, exclusivity, reimbursement-related issues); contracting and purchasing strategies to address drug shortages; and increasing the availability of unit-of-use packaging. See the Appendix for a summary of potential “solutions” addressing drug shortages that emerged from this Summit.

CONCLUSION

Drug shortages continue to exist and easy solutions remain elusive. Manufacturers are notifying the FDA about potential disruptions in supply or shortages earlier than in the past and new shortages are being prevented. This has led to significant reduction in the total number of new drug shortages, but some long term shortages persist and continue to impact clinical decision-making and patient care. Only five major companies are now producing sterile injectable products, and concurrent remediation efforts are in place to upgrade facilities among them.

Most drug shortages continue to be related to lack of manufacturing capacity coupled with quality problems, either at the manufacturing facility or that become apparent in the final product itself, such as contamination with glass, metal, mold, or bacteria. Although manufacturers are building new facilities, upgrading equipment and increasing capacity for generic sterile injectable products, this will take several years to complete and secure the necessary approvals from global regulators. Compared with brand name manufacturers that typically devote a single production line to a product, companies that manufacture sterile injectables typically make multiple products on a single production line, except where this practice is restricted or prohibited because of the product itself (e.g., antibiotics, chemotherapeutic agents).

A number of existing efforts are directed toward addressing quality, regulatory, and economic issues underlying drug shortages and a number of potential measures to address shortages also have been advanced. The AMA remains committed to supporting appropriate long term solutions to the drug shortage problem.

RECOMMENDATIONS

The Council on Science and Public Health recommends that Policy H-100.956 be amended by addition and deletion to read as follows:

H-100.956 National Drug Shortages

1. Our AMA supports ~~the~~ recommendations that have been developed by multiple stakeholders to improve manufacturing quality systems, identify efficiencies in regulatory review that can mitigate drug shortages, and explore measures designed to drive greater investment in production capacity for products that experience drug shortages of the 2010 Drug Shortage Summit convened by the American Society of Health System Pharmacists, American Society of Anesthesiologists, American Society of Clinical Oncology and the Institute for Safe Medication Practices and will work in a collaborative fashion with these and other stakeholders to implement these recommendations in an urgent fashion.

~~2. Our AMA supports requiring all manufacturers of Food and Drug Administration approved drugs and, including FDA approved drugs with recognized off label uses, to give the agency advance notice (at least 6 months prior or otherwise as soon as practicable) of anticipated voluntary or involuntary, permanent or temporary, discontinuance of the manufacture or marketing of such a product.~~

~~3.~~ 2. Our AMA supports authorizing the Secretary of Health and Human Services to expedite facility inspections and the review of manufacturing changes, drug applications and supplements that would help mitigate or prevent a drug shortage.

~~4. Our AMA supports the creation of a task force to enhance the HHS Secretary’s response to preventing and mitigating drug shortages and to create a strategic plan to: (a) enhance interagency coordination; (b) address~~

~~drug shortage possibilities when initiating regulatory actions (including the removal of unapproved drug products from the market); (c) improve FDA's ability to track and analyze drug shortage data in an effort to develop strategies to better prevent drug shortages (d) provide further information on expedited solutions that have worked to prevent or mitigate drug shortages; (e) communicate with stakeholders; and (f) consider the impact of drug shortages on research and clinical trials.~~

53. Our AMA will advocate that the U.S. Food and Drug Administration and/or Congress require drug manufacturers to establish a plan for continuity of supply of vital and life-sustaining medications and vaccines to avoid production shortages whenever possible. This plan should include establishing the necessary resiliency and redundancy in manufacturing capability to minimize disruptions of supplies in foreseeable circumstances including the possibility of a disaster affecting a plant.

64. The Council on Science and Public Health shall continue to evaluate the drug shortage issue and report back at least annually to the House of Delegates on progress made in addressing drug shortages.

75. Our AMA urges the development of a comprehensive independent report on the root causes of drug shortages. Such an analysis should consider federal actions, the number of manufacturers, economic factors including federal reimbursement practices, as well as contracting practices by market participants on competition, access to drugs, and pricing. In particular, further transparent analysis of economic drivers is warranted. The Centers for Medicare & Medicaid Services should review and evaluate its 2003 Medicare reimbursement formula of average sales price plus 6% for unintended consequences including serving as a root cause of drug shortages.

~~8. Our AMA urges that procedures be put in place: (1) for the FDA to monitor the availability of Schedule II controlled substances; (2) for the FDA to identify the existence of a shortage that is caused or exacerbated by existing production quotas; and, (3) for expedited DEA review of requests to increase aggregate and individual production quotas for such substances.~~

96. Our AMA urges regulatory relief designed to improve the availability of prescription drugs by ensuring that such products are not removed from the market due to compliance issues unless such removal is clearly required for significant and obvious safety reasons.

107. Our AMA supports the view that wholesalers should routinely institute an allocation system that attempts to fairly distribute drugs in short supply based on remaining inventory and considering the customer's purchase history.

118. Our AMA will collaborate with medical specialty partners in identifying and supporting legislative remedies to allow for more reasonable and sustainable payment rates for prescription drugs. (CSAPH Rep. 2, I-11; Modified: CSAPH Rep. 7, A-12; Modified: CSAPH Rep. 2, I-12; Modified: CSAPH Rep. 8, A-13; Modified in lieu of Res. 912, I-13; Modified: CSAPH Rep. 3, A-14) (Amend HOD Policy)

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Table 1. Contrasting the FDA (CDER) and ASHP Drug Shortage Websites

	FDA	ASHP
Purpose	Provides information obtained from manufacturers about current shortages, estimated duration, and discontinuations and provides information about FDA’s and other stakeholders’ roles in addressing and preventing shortages	Notification of new shortages and status of ongoing shortages; drug shortage management resources
Audience	Public	Healthcare practitioners
Scope of shortage list	All drugs are listed that are confirmed to be a national shortage by FDA. A shortage is considered to be the period of time when the demand for the drug within the United States exceeds the supply of the drug. ^c	All drug and biologic shortages reported and confirmed with manufacturer that are national in impact.
Source of shortage report	Manufacturers notify FDA of production disruption and voluntarily provide updates. Reports are also received from ASHP and from public via drugshortages@cderr.fda.gov Note: Manufacturer-provided information represents shortage status at drug firm level.	Voluntary reports from practitioners, patients, pharmaceutical industry representatives and others Note 1: Information is updated based on release dates from manufacturers. Note 2: Reports reflect status at healthcare provider level.
Criteria for inclusion on list	Manufacturers cannot meet current market demand for the drug based on information provided by manufacturers and market sales research. Drug listed are defined as “medically necessary.”	(1) Shortage is verified with manufacturers and (2) affects how pharmacy prepares or dispenses a product, or (3) requires use of alternative drugs, which may affect patient care.

^c Note: A separate shortage webpage for vaccines and some biologics is maintained by the Center for Biologics Evaluation and Research.

Criteria for resolving shortage	One or more manufacturers are in production and able to meet full market demand.	All manufacturers of the drug restore all formulations and dosage sizes to full availability. Note: Products are listed despite partial or restricted availability as supply chain disruptions can result in intermittent shortages at the provider or patient level.
Reason for shortage	Provided by manufacturers using reasons required by legislation. ^f FDA encourages firms to provide additional information about reasons and other information which, if proprietary, is nondisclosable without the firm's permission.	Provided by manufacturer, if willing to disclose. Note: May differ from FDA's due to different sources of information and legislation requiring FDA to use specified reasons
Other information	Estimated duration, links to regulatory information such as recalls and Dear Healthcare Provider Letters	Estimated duration, list of available products, implications for patient care and safety, shortage management strategies, therapeutic alternatives

APPENDIX²²

	FDA	ASHP
Purpose	Provides information obtained from manufacturers about current shortages, estimated duration, and discontinuations and provides information about FDA's and other stakeholders' roles in addressing and preventing shortages	Notification of new shortages and status of ongoing shortages; drug shortage management resources
Audience	Public	Healthcare practitioners
Scope of shortage list	All drugs are listed that are confirmed to be a national shortage by FDA. A shortage is considered to be the period of time when the demand for the drug within the United States exceeds the supply of the drug. ^g	All drug and biologic shortages reported and confirmed with manufacturer that are national in impact.
Source of shortage report	Manufacturers notify FDA of production disruption and voluntarily provide updates. Reports are also received from ASHP and from public via drugshortages@cdcr.fda.gov Note: Manufacturer-provided information represents shortage status at drug firm level.	Voluntary reports from practitioners, patients, pharmaceutical industry representatives and others Note 1: Information is updated based on release dates from manufacturers. Note 2: Reports reflect status at healthcare provider level.
Criteria for inclusion on list	Manufacturers cannot meet current market demand for the drug based on information provided by manufacturers and market sales research. Drug listed are defined as "medically necessary."	(1) Shortage is verified with manufacturers and (2) affects how pharmacy prepares or dispenses a product, or (3) requires use of alternative drugs, which may affect patient care.
Criteria for resolving shortage	One or more manufacturers are in production and able to meet full market demand.	All manufacturers of the drug restore all formulations and dosage sizes to full availability. Note: Products are listed despite partial or restricted availability as supply chain disruptions can result in intermittent shortages at the provider or patient level.
Reason for shortage	Provided by manufacturers using reasons required by legislation. ^h FDA encourages firms to provide additional information about reasons and other information which, if proprietary, is nondisclosable without the firm's permission.	Provided by manufacturer, if willing to disclose. Note: May differ from FDA's due to different sources of information and legislation requiring FDA to use specified reasons
Other information	Estimated duration, links to regulatory information such as recalls and Dear Healthcare Provider Letters	Estimated duration, list of available products, implications for patient care and safety, shortage management strategies, therapeutic alternatives

^f Categories include (a) requirement related to complying with good manufacturing practices; (b) regulatory delay; (c) shortage of an active ingredient

^g Note: A separate shortage webpage for vaccines and some biologics is maintained by the Center for Biologics Evaluation and Research.

^h Categories include (a) requirement related to complying with good manufacturing practices; (b) regulatory delay; (c) shortage of an active ingredient

3. COMBATING ANTIBIOTIC RESISTANCE: AN UPDATE

Reference committee hearing: see report of [Reference Committee K](#).

**HOUSE ACTION: RECOMMENDATIONS ADOPTED
REMAINDER OF REPORT FILED**

See Policies H-100.952, H-100.953, H-100.960, H-100.973, H-440.827,
H-440.834, H-440.846 and D-100.998

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 US 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 US 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.

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 facilities 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.

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.
 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.

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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.

H-100.953 Establishment of Limited Population Antibacterial Drug Approval Pathway

1. Our AMA supports establishment of the Limited Population Antibacterial Drug (LPAD) 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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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. 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.

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

