A PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE

PART 1: DOMESTIC ISSUES

Interagency Task Force on Antimicrobial Resistance

Co-chairs:

Centers for Disease Control and Prevention

Food and Drug Administration

National Institutes of Health

Agency for Healthcare Research and Quality

Health Care Financing Administration

Health Resources and Services Administration

Department of Agriculture

Department of Defense

Department of Veterans Affairs

Environmental Protection Agency

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A Public Health Action Plan to Combat Antimicrobial Resistance
Executive Summary

This *Public Health Action Plan to Combat Antimicrobial Resistance* (*Action Plan*) was developed by an interagency Task Force on Antimicrobial Resistance that was created in 1999. The Task Force is co-chaired by the Centers for Disease Control and Prevention, the Food and Drug Administration, and the National Institutes of Health and also includes the Agency for Healthcare Research and Quality, the Health Care Financing Administration, the Health Resources and Services Administration, the Department of Agriculture, the Department of Defense, the Department of Veterans Affairs, and the Environmental Protection Agency.

The *Action Plan* reflects a broad-based consensus of federal agencies on actions needed to address antimicrobial[a] resistance (AR). Input from state and local health agencies, universities, professional societies, pharmaceutical companies, health care delivery organizations, agricultural producers, consumer groups, and other members of the public was important in developing the plan. While some actions are already underway, complete implementation of this plan will require close collaboration with all of these partners,[b] a major objective of the process. The plan will be implemented incrementally, dependent on the availability of resources.

The *Action Plan* provides a blueprint for specific, coordinated federal actions to address the emerging threat of antimicrobial resistance. This document is Part I of the *Action Plan*, focusing on domestic issues. Since AR transcends national borders and requires a global approach to its prevention and control, Part II of the plan, to be developed subsequently, will identify actions that more specifically address international issues. The *Action Plan*, Part I (Domestic Issues), includes four focus areas: Surveillance, Prevention and Control, Research, and Product Development. A summary of the top priority goals and action items in each focus area follows.

Surveillance

Unless AR problems are detected as they emerge B and actions are taken quickly to contain them B the world may soon be faced with previously treatable diseases that have again become untreatable, as in the pre-antibiotic era. Priority Goals and Action Items in this focus area address ways to:

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[a]In this document, the term Aantimicrobial@ is used inclusively to refer to any agent (including an antibiotic) used to kill or inhibit the growth of microorganisms (bacteria, viruses, fungi, or parasites). This term applies whether the agent is intended for human, veterinary or agricultural applications.

[b]Implementation of this *Action Plan* requires working with a wide variety of partners, e.g., state and local health agencies, universities, professional societies, pharmaceutical and biotechnology companies, health care delivery organizations, insurers, agricultural producers, consumer groups, and the public. A wide variety of expertise is needed, e.g., from clinicians, consumers, pharmacists, microbiologists, epidemiologists, behavioral and social scientists, economists, health policy researchers, and others. Partners and expertise needed will vary with different action items.

- Develop and implement a coordinated national plan for AR surveillance;
- Ensure the availability of reliable drug susceptibility data for surveillance;
- Monitor patterns of antimicrobial drug use; and
- Monitor AR in agricultural settings to protect the public=s health by ensuring a safe food supply as well as animal and plant health.

A coordinated national surveillance plan for monitoring AR in microorganisms that pose a threat to public health will be developed and implemented. The plan will specify activities to be conducted at national, state, and local levels; define the roles of participants; promote the use of standardized methods; and provide for timely dissemination of data to interested parties, e.g., public health officials, clinicians, and researchers. Needed core capacities at state and local levels will be defined and supported. When possible, the plan will coordinate, integrate, and build on existing disease surveillance infrastructure. All surveillance activities will be conducted with respect for patient and institutional confidentiality.

The availability of reliable drug susceptibility data is essential for AR surveillance. The accuracy of AR detection and reporting will be improved through training and proficiency testing programs for diagnostic laboratories and by promoting and further refining standardized methods for detecting drug resistance in important pathogens, including bacteria, parasites, fungi, and viruses. Public and private sector partners will address barriers to AR testing and reporting, e.g., barriers due to changes in health care delivery.

A plan to monitor patterns of antimicrobial drug use will be developed and implemented as an important component of the national AR surveillance plan. This information is essential to interpret trends and variations in rates of AR, improve our understanding of the relationship between drug use and resistance, identify and anticipate gaps in availability of existing drugs, and identify interventions to prevent and control AR.

Improved surveillance for AR in agricultural settings will allow early detection of resistance trends in pathogens that pose a risk to animal and plant health, as well as in bacteria that enter the food supply. Agricultural surveillance data will also help improve understanding of the relationship between antimicrobial drug and pesticide use and the emergence of drug resistance.

Prevention and Control

The prevention and control of drug-resistant infections requires measures to promote the appropriate use[c] of antimicrobial drugs and prevent the transmission of infections (whether drug-resistant or not). Priority Goals and Action Items in this focus area address ways to:

[c]In this *Action Plan*, appropriate antimicrobial drug use is defined as use that maximizes therapeutic impact while minimizing toxicity and the development of resistance. In practice, this means prescribing antimicrobial therapy when and only when beneficial to a patient; targeting therapy to the desired pathogens; and using the appropriate drug, dose, and duration.

- < Extend the useful life of antimicrobial drugs through appropriate use policies that discourage overuse and misuse;
- < Improve diagnostic testing practices;
- < Prevent infection transmission through improved infection control methods and use of vaccines;
- < Prevent and control emerging AR problems in agriculture, human and veterinary medicine; and
- < Ensure that comprehensive programs to prevent and control AR involve a wide variety of nonfederal partners and the public so these programs become a part of routine practice nationwide.

Appropriate drug-use policies will be implemented through a public health education campaign on appropriate antimicrobial drug use as a national health priority. Other actions in support of appropriate drug use will include reducing inappropriate prescribing through development of clinical guidelines and computer-assisted decision support, considering regulatory changes, supporting other interventions promoting education and behavior change among clinicians, and informing consumers about the uses and limitations of antimicrobial drugs.

Improved diagnostic practices will be promoted by encouraging the use of rapid diagnostic methods to guide drug prescribing, facilitating direct consultation between clinicians and laboratory personnel with appropriate expertise and authority, and promoting the use of appropriate laboratory testing methods. Guidelines, training, and regulatory and reimbursement policies will be utilized to promote improved diagnostic practices.

Reduced rates of infection transmission will be addressed through public health campaigns that promote vaccination and hygienic practices such as hand washing, safe food handling, and other behaviors associated with prevention of infection transmission. Infection control in health care settings will be enhanced by developing new interventions based on rapid diagnosis, improved understanding of the factors that promote cross-infection, and modified medical devices or procedures that reduce the risk of infection.

The prevention and control of AR in agriculture and veterinary medicine requires 1) improved understanding of the risks and benefits of antimicrobial use and ways to prevent the emergence and spread of resistance; 2) development and implementation of principles for appropriate antimicrobial drug use in the production of food animals and plants; 3) improved animal husbandry and food-production practices to reduce the spread of infection; and 4) a regulatory framework to address the need for antimicrobial drug use in agriculture and veterinary medicine while ensuring that such use does not pose a risk to human health.

Comprehensive, multifaceted programs involving a wide variety of nonfederal partners and the public are required to prevent and control AR. The AR Task Force agencies will ensure ongoing input from, review by, and collaboration with nonfederal partners. The appropriate agencies will support demonstration projects that use multiple interventions to prevent and control AR (e.g., through surveillance, appropriate drug use, optimized diagnostic testing, immunization practice,

and infection control). The Task Force agencies will encourage the incorporation of effective programs into routine practice by implementing model programs in federal health care systems and promoting the inclusion of AR prevention and control activities as part of quality assurance and accreditation standards for health care delivery nationwide.

Research

Understanding the fundamental processes involved in antimicrobial resistance within microbes and the resulting impact on humans, animals, and the environment forms an important basis for influencing and changing these processes and outcomes. Basic and clinical research provides the fundamental knowledge necessary to develop appropriate responses to antimicrobial resistance emerging and spreading in hospitals, communities, farms, and the food supply. Priority Goals and Action Items in this focus area address ways to:

- Increase understanding of microbial physiology, ecology, genetics and mechanisms of resistance;
- Augment the existing research infrastructure to support a critical mass of researchers in AR and related fields; and
- Translate research findings into clinically useful products, such as novel approaches to detecting, preventing, and treating antimicrobial resistant infections.

Needs in the field of AR research will be identified and addressed through a government-wide program review with external input. Additional research is needed, for example, on the epidemiology of resistance genes; on mechanisms of AR emergence, acquisition, spread, and persistence; and on the effects of antibiotics used as agricultural growth promotants on microbes that live in animals, humans, plants, soil and water. Further study is also required to determine whether variations in drug use regimens may stimulate or reduce AR emergence and spread. Improved understanding of the causes of AR emergence will lead to the development of tools for reducing microbial resistance, as well as for predicting where AR problems are likely to arise.

A comprehensive research infrastructure will help ensure a critical mass of AR researchers who will interact, exchange information, and stimulate new discoveries. This aim will be achieved through the appropriate strategies and scientific conferences that promote research on AR. The AR Task Force agencies will work with the academic and industrial research communities to attract AR researchers, prioritize needs, identify key opportunities, and optimize the utilization of resources to address AR problems.

The translation of research findings into innovative clinical products to treat, prevent, or diagnose drug-resistant infections is an area in which the federal government can play an important role, focusing on gaps not filled by the pharmaceutical industry or by other nongovernment groups. Special efforts will be placed on the identification, development and testing of rapid, inexpensive, point-of-care diagnostic methods to facilitate appropriate use of antimicrobials. The AR Task Force agencies will also encourage basic research and clinical testing of diagnostic methods, novel treatment approaches, new vaccines, and other prevention approaches for resistant infections.

Product Development

As antimicrobial drugs lose their effectiveness, new products must be developed to prevent, rapidly diagnose, and treat infections. The Priority Goals and Action Items in this focus area address ways to:

- Ensure that researchers and drug manufacturers are informed of current and projected gaps in the arsenal of antimicrobial drugs, vaccines, and diagnostics and of potential markets for these products (designated here as AAR products@);
- Stimulate the development of priority AR products for which market incentives are inadequate, while fostering their appropriate use; and
- Optimize the development and use of veterinary drugs and related agricultural products that reduce the transfer of resistance to pathogens that can infect humans.

Current and projected gaps in the arsenal of AR products and potential markets for these products will be reported to researchers and drug manufacturers through an interagency working group convened to identify and publicize priority public health needs.

The development of urgently needed AR products will be stimulated throughout the process from drug discovery through licensing. The regulatory process for AR products will continue to be streamlined, and incentives that promote the production and appropriate use of priority AR products can be evaluated in pilot programs that monitor costs and assess the return on the public investment.

The production of veterinary AR products that reduce the risk of development and transfer of resistance to drugs used in human clinical medicine will be expedited through a streamlined regulatory and approval process. As with drugs for the treatment of human infections, pilot programs can be initiated to evaluate incentives that encourage the development and appropriate use of priority products that meet critical animal and plant health needs.

Private and public partners will also evaluate ways to improve or reduce the agricultural use of particular antimicrobial drugs, as well as ways to prevent infection, such as the use of veterinary vaccines, changes in animal husbandry, and the use of competitive exclusion products (i.e., treatments that affect the intestinal flora of food animals).

Top Priority Action Items to Combat Antimicrobial Resistance
(All 13 items have top priority, regardless of their order in the list)

Surveillance

- With partners, design and implement a national AR surveillance plan that defines national, regional, state, and local surveillance activities and the roles of clinical, reference, public health, and veterinary laboratories. The plan should be consistent with local and national surveillance methodology and infrastructure that currently exist or are being developed.
  (Action Item #2)

- Develop and implement procedures for monitoring patterns of antimicrobial drug use in human medicine, agriculture, veterinary medicine, and consumer products.
  (Action Item #5)

Prevention and Control

- Conduct a public health education campaign to promote appropriate antimicrobial use as a national health priority.
  (Action Item #25)

- In collaboration with many partners, develop and facilitate the implementation of educational and behavioral interventions that will assist clinicians in appropriate antimicrobial prescribing.
  (Action Item #26)

- Evaluate the effectiveness (including cost-effectiveness) of current and novel infection-control practices for health care and extended care settings and in the community. Promote adherence to practices proven to be effective.
  (Action Item #39)

- In consultation with stakeholders, refine and implement the proposed FDA framework for approving new antimicrobial drugs for use in food-animal production and, when appropriate, for re-evaluating currently approved veterinary antimicrobial drugs.
  (Action Item #58)

- Support demonstration projects to evaluate comprehensive strategies that use multiple interventions to promote appropriate drug use and reduce infection rates, in order to assess how interventions found effective in research studies can be applied routinely and most cost-effectively on a large scale.
  (Action Item #63)

Research

- Provide the research community genomics and other powerful technologies to identify targets in critical areas for the development of new rapid diagnostics methodologies, novel therapeutics, and interventions to prevent the emergence and spread of resistant pathogens.
  (Action Item #70)

- In consultation with academia and the private sector, identify and conduct human clinical studies addressing AR issues of public health significance that are unlikely to be studied in the private sector (e.g., novel therapies, new treatment regimens, and other products and practices).
  (Action Item #75)

- Identify, develop, test, and evaluate new rapid diagnostic methods for human and veterinary uses with partners, including academia and the private sector. Such methods should be accurate, affordable, and easily implemented in routine clinical settings (e.g., tests for resistance genes, point-of-care diagnostics for patients with respiratory infections and syndromes, and diagnostics for drug resistance in microbial pathogens, including in nonculture specimens).
  (Action Item #76)

- Encourage basic and clinical research in support of the development and appropriate use of vaccines in human and veterinary medicine in partnership with academia and the private sector.
  (Action Item #77)

Product Development

- Create an Interagency AR Product Development Working Group to identify and publicize priority public health needs in human and animal medicine for new AR products (e.g., innovative drugs, targeted spectrum antibiotics, point-of-care diagnostics, vaccines and other biologics, anti-infective medical devices, and disinfectants).
  (Action Item #79)

- Identify ways (e.g., financial and/or other incentives or investments) to promote the development and/or appropriate use of priority AR products, such as novel compounds and approaches, for human and veterinary medicine for which market incentives are inadequate.
  (Action Item #80)

Introduction and Overview

Background

In the 1940s, the widespread availability of penicillin and the subsequent discovery of streptomycin led to a dramatic reduction in illness and death from infectious diseases. However, bacteria and other disease-causing organisms **B** viruses, fungi, and parasites **B** have a remarkable ability to mutate and acquire resistance genes from other organisms and thereby develop resistance to antimicrobial drugs. When an antimicrobial drug is used, the selective pressure exerted by the drug favors the growth of organisms that are resistant to the drug=s action. The extensive use of antimicrobial drugs has resulted in drug resistance that threatens to reverse the miracles of the last half century.

Drug-resistant pathogens are a growing menace to all people, regardless of age, gender, or socioeconomic background. They endanger people in affluent, industrial societies like the United States, as well as in less developed nations. Examples of clinically important microbes that are rapidly developing resistance to available antimicrobials include bacteria that cause pneumonia, ear infections, and meningitis (e.g., *Streptococcus pneumoniae*[1]), skin, bone, lung, and bloodstream infections (e.g., *Staphylococcus aureus*[2,3]), urinary tract infections (e.g., *Escherichia coli*[4]), foodborne infections (e.g., *Salmonella*[5]), and infections transmitted in health care settings (e.g., enterococci[6] and *Klebsiella* spp.[7]).

For example, up to 30 percent of *S. pneumoniae* found in some areas of the United States are no longer susceptible to penicillin, and multidrug resistance is common. Approximately 11 percent of *S. pneumoniae* are resistant to Athird generation@ cephalosporin antibiotics, and resistance to the newest fluoroquinolone antimicrobials has already been reported.[8] Nearly all strains of *Staphylococcus aureus* in the United States are resistant to penicillin, and many are resistant to newer methicillin-related drugs.[2] Since 1997, strains of *S. aureus* with decreased susceptibility to vancomycin, for many years the only uniformly effective treatment, have been reported.[9,10]

Many other pathogens **B** including the bacteria that cause tuberculosis[11] and gonorrhea,[12] human immunodeficiency virus,[13] the fungi that cause yeast infections,[14] and the parasites that cause malaria[15] **B** are also becoming resistant to standard therapies. If we do not act to address the problem of AR, we may lose quick and reliable treatment of infections that have been a manageable problem in the United States since the 1940s. Drug choices for the treatment of common infections will become increasingly limited and expensive **B** and, in some cases, nonexistent.

Risk

While anyone may acquire a drug-resistant infection, certain people are at increased risk, e.g., patients in hospitals and children in daycare centers. Drug-resistant infections may be acquired in health care settings (e.g., staphylococcal infections in intensive care units), in the community (e.g., pneumococci acquired from a classmate) and through the food supply (e.g., salmonella

acquired from meat or eggs), both domestically and overseas. However, resistant microbes are increasingly appearing in new settings. Methicillin-resistant *S. aureus*, which for 30 years with few exceptions was a problem only in hospitals, is now occurring in the community.[3,16]

Costs

The costs of treating AR infections place a significant burden on society **B** a burden that is likely to grow larger as the number of cases of drug-resistant illness increase. Individuals infected with drug resistant organisms are more likely to require hospitalization, to remain in the hospital for a longer time, and to have a poor prognosis. For example, it has been estimated that the in-hospital cost of hospital-acquired infections caused by just six common kinds of resistant bacteria are at least $1.3 billion per year, in 1992 dollars.[17] This estimate does not include the costs of infections caused by other pathogens, the costs of lost workdays, post-hospital care, or resistant infections in the outpatient or extended care facility settings.

Solutions

AR will always be with us. The challenge before us is to transform this increasingly urgent threat into a manageable problem. Over the past ten years, the Institute of Medicine,[18] the American Society for Microbiology,[19] World Health Organization[20] other panels of distinguished experts, the Congressional Office of Technology Assessment,[17] and the General Accounting Office[21, 22] have provided recommendations and options for government action to address the dangers posed by AR. The experts agree that we need to improve surveillance for emerging AR problems, to prolong the useful life of antimicrobial drugs, to develop new drugs, and to utilize other measures, e.g., improved vaccines, diagnostics, and infection control measures to prevent and control AR.

Despite the urgency of the problem, the achievement of these goals has not been simple or straightforward, and accomplishments to date have been insufficient. Monitoring, preventing, and controlling AR requires sustained effort, commitment, and collaboration among many groups in the public and private sectors, and involvement of the general public. It also requires support and leadership from the federal government and a willingness to address complex and sometimes controversial scientific, medical, and economic issues.

A Public Health Action Plan to Combat Antimicrobial Resistance

A Public Health Action Plan to Combat Antimicrobial Resistance provides a blueprint for specific, coordinated federal government actions to address this emerging threat. The plan builds upon reports prepared by expert panels in recent years. This document is Part I of the plan, focusing on domestic issues. However, AR transcends national borders and requires a global approach to its prevention and control. Part II of the plan, to be developed after the World Health Organization finalizes its Global Strategy for the Containment of Antimicrobial Resistance,[23] will identify federal actions that more specifically address international issues with input from and in collaboration with WHO and additional partners. *A National Action Plan to Combat Multi-drug Resistant Tuberculosis* has been published previously.[24]

Plan Development

This plan was developed by an Interagency Task Force on Antimicrobial Resistance that was created in 1999. The Task Force is co-chaired by the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH), and also includes the Agency for Healthcare Research and Quality (AHRQ), the Health Care Financing Administration (HCFA), the Health Resources and Services Administration (HRSA), the Department of Agriculture (USDA), the Department of Defense (DoD), the Department of Veterans Affairs (DVA), and the Environmental Protection Agency (EPA).

The plan is based in part on input obtained at a public meeting held in Atlanta, Georgia, in July 1999.[25] Present at the public meeting were consultants from a wide variety of groups, including state and local health agencies, universities, professional societies, pharmaceutical and biotechnology companies, health care delivery organizations, agricultural producers, consumer groups, and the public. A draft of the plan was released for public comment in June 2000,[26] and the plan was modified following consideration of comments received.

Partnerships, Implementation, and Coordination

The plan reflects a broadly based consensus of federal agencies on federal actions to combat AR. However, implementation of this plan will require collaboration with many partners.[b] More specific details of these collaborations will be developed by the agencies as the actions are implemented.

The plan will be implemented incrementally as resources become available. The agencies recognize that a number of the items may require either new statutory authority or changes in regulatory requirements. The extent to which such measures may be needed to implement a given action item will be considered by the agencies involved.

The plan includes a summary and a list of issues, goals, and action items addressing surveillance, prevention and control, research, and product development.[d] For each action item, coordinator and collaborator agencies/departments are specified. Contingent on available resources, the coordinators will assume the primary responsibility of carrying out the specified action items and the collaborators will assist and/or carry out part of the specified action. Additional agencies may become collaborators in the future.

The Task Force identified 13 top priority action items. Approximate timelines were also identified for all action items; these timelines provide another indication of priority but also take into account prerequisites for certain items and the achievable pace of action on sometimes complex issues. Designation of top priorities and timelines was a difficult task given the realization that many items could be considered top priority and should ideally begin

[d]Except where specified, these issues, goals, and action items apply to human AR issues and not to nonhuman (e.g., agricultural) issues. Agricultural issues refer to the production of animals and plants, as well as fish and other species (aquaculture).

immediately. For action items with multiple component parts, the agencies involved will further develop priorities and timelines, with appropriate input from outside partners, as they implement the action item.

The Interagency Task Force will continue to facilitate coordination among agencies and monitor implementation of the plan. During the coming years, the Task Force will publish periodic reports detailing how the plan is being implemented, solicit comments from the public, **B** and if necessary, update the plan. Details of current agency activities regarding AR are beyond the scope of this document, but may be obtained by contacting the specific agencies.

The Focus Areas

I. Surveillance

Surveillance of AR is critical to providing early warning of emerging problems, monitoring changing patterns of resistance, and targeting and evaluating prevention and control measures.[e] Timely surveillance information is also necessary for assisting researchers in developing new drugs and for providing good patient care. For example, clinicians should be informed of drug resistance problems in their communities that may influence their prescribing decisions in order to help them avoid treatment failures. In addition, monitoring patterns of antimicrobial drug use is needed to interpret trends and variations in rates of AR, improve understanding of the relationship between drug use and resistance, identify and anticipate gaps in availability of existing drugs, and help identify preventive interventions.

At present, the United States lacks a coordinated national plan for AR surveillance. Creating a national plan requires collaboration with partners in the public and private sectors. Improved AR surveillance depends on enhancing epidemiologic and laboratory capabilities at local, state, and national levels; using standardized and reliable laboratory testing methods; and enhancing use of informatics.

A. Issue: The United States lacks a coordinated national plan for surveillance of:
- **$** AR emergence in organism-drug combinations of public health importance and
- **$** Antimicrobial drug use in human and nonhuman settings.

1. Goal: Collaborate with appropriate partners to develop procedures and methods for surveillance of AR emergence in organism-drug combinations of public health importance.

a. Action Items

(1) Determine which organisms and susceptibility to specific antimicrobial drugs should be under surveillance and create a mechanism for periodic updating of this list.
Coordinators: CDC, FDA, USDA, EPA
Timeline: Initiated

[e]Public health surveillance is the ongoing, systematic collection, analysis, and interpretation of data for use in the planning, implementation, and evaluation of public health practice. Desirable qualities of any system include simplicity, flexibility, acceptability, sensitivity, and representativeness. A surveillance system also includes the timely dissemination of these data to persons who can undertake effective prevention and control activities, including clinicians, researchers, laboratorians, and public health personnel. (MMWR, Guidelines for Evaluating Surveillance Systems, May 6, 1988/37(S5); 118.)

(2) **TOP PRIORITY ACTION ITEM** - With partners, design and implement a national AR surveillance plan:

- **$** Identify the components of a national AR surveillance plan and the roles of partners in its design and implementation.
  Coordinator: CDC; Collaborators: DoD, DVA, FDA, USDA, HCFA
- **$** Determine which surveillance activities should be conducted routinely at national, regional, state, or local levels and which may require specialized projects.
  Coordinators: CDC, FDA, USDA
- **$** Define the roles of clinical, reference, public health, and veterinary laboratories at federal, state, and local levels in AR surveillance.
  Coordinator: CDC; Collaborators: DoD, DVA, FDA, USDA, HCFA
- **$** Improve coordination of AR surveillance systems at CDC, FDA, and USDA (e.g., identify components for integration).
  Coordinators: CDC, FDA, USDA
- **$** Consider the role of nongovernment-funded surveillance and other data collection systems to augment a national surveillance plan.
  Coordinators: CDC, FDA, USDA
- **$** Ensure that the national AR surveillance plan is consistent with local and national surveillance methodology and infrastructure that currently exist or are being developed.
  Coordinators: CDC, USDA, FDA
- **$** Identify and assess practical surveillance strategies for components of the national plan by conducting pilot studies and demonstration projects.
  Coordinators: CDC, USDA, FDA

Timeline for entire action item 2: Begin within one to two years

(3) Develop standards and methodologies.

- **$** Develop standards and methodologies for monitoring drug-resistant microbes in humans, animals, and plants as well as for monitoring drug-resistant microbes in food products and environmental samples.
  Coordinators: CDC, UDSA, FDA, EPA
- **$** Develop standardized laboratory methodologies and data elements that allow susceptibility test results and AR surveillance data to be compared across geographic jurisdictions.
  Coordinators: CDC, USDA, FDA, EPA
- **$** Explore the use of standardized definitions and methodology (Related Action Item: Surveillance #5) to create an electronic surveillance system health care institutions can use to compare AR data from other local facilities.
  Coordinator: CDC; Collaborators: HCFA, DVA, DoD, HRSA
- **$** Encourage development of local, regional, and national data systems that allow linking of microbiology, clinical and pharmaceutical data that would support local decision making for prevention and control of antimicrobial

resistance and facilitate surveillance for antimicrobial resistance at all levels.
Coordinator: CDC; Collaborators: HCFA, DVA, DoD, HRSA

- **$** Develop standards for reporting quantitative resistance data (e.g., minimal inhibitory concentrations or zone diameters) in ways that will detect decreased susceptibility. These standards are necessary because numerical AR test results reported nonquantitatively (e.g., as susceptible, intermediate, or resistant) as Asusceptible@ may mask an emerging AR problem, i.e., microbes with a small decrease in susceptibility may still be classified as susceptible.
  Coordinators: CDC, USDA, FDA
- **$** Assess how current policies on maintaining the confidentiality of medical and veterinary data collected for other purposes relate to procedures for gathering data on antimicrobial resistance. If necessary, develop a comprehensive national confidentiality policy on human and agricultural AR surveillance that includes both patient and institutional confidentiality, is consistent with confidentiality policies applied to other forms of surveillance and research data, and recognizes the differences in human and animal medicine and food production surveillance programs.
  Coordinator: CDC; Collaborators: DVA, HCFA, DoD, FDA, USDA
  Timeline for entire action item 3: Initiated

(4) Address additional surveillance issues unique to AR.

- **$** Conduct post-marketing surveillance for the development of resistance to critical antimicrobial drugs. Surveillance should be linked to information on drug use, and criteria should be developed to allow a prompt response to a finding of increased resistance associated with a specific pattern of use (e.g., consumer and professional alerts, enhanced education, labeling changes, or restrictions on use depending on the extent of and reasons for emergence of resistance).
  Coordinators: FDA, CDC, USDA
- **$** Facilitate the collection of AR surveillance data on pathogens for which cultures are not routinely obtained, either because the infections are empirically treated without laboratory diagnosis or because they are diagnosed with nonculture tests.
  Coordinator: CDC
- **$** Enhance availability of isolates of drug-resistant microbes to researchers (e.g., via a network of collections with an accessible databank).
  Coordinator: CDC; Collaborator: NIH
  Timeline for entire action item 4: Begin within one to two years

2. Goal: Collaborate with appropriate partners to develop procedures and methods for nationwide surveillance of antimicrobial drug use in human and nonhuman settings.

a. Action Items

(5) **TOP PRIORITY ACTION ITEM** - Develop and implement procedures for monitoring antimicrobial use in human medicine, agriculture, veterinary medicine, and consumer products:

- **$** Link human drug-use data to clinical information (e.g., diagnosis, severity of illness, and outcome).
- **$** Link agricultural drug-use data to species and usage patterns.
- **$** Assess potential effects of geographic variations in drug use on the incidence and prevalence of antimicrobial resistance.
- **$** Incorporate appropriate confidentiality protections.
- **$** Identify and anticipate gaps in availability of existing drugs. (Related Action Item: Product Development #79).

Coordinators: CDC, FDA, USDA; Collaborators: EPA, DVA, DoD
Timeline for entire action item 5: Begin within one to two years

(6) Identify and evaluate methods for collecting (e.g., optimal sampling methods) and disseminating the surveillance data on antimicrobial drug use:

- **$** Identify inexpensive sources of drug use data (e.g., the National Ambulatory Medical Care Survey [NAMCS], the National Hospital Ambulatory Medical Care Survey [NHAMCS], and databases in some health care delivery systems and pharmacies) and evaluate their usefulness for surveillance purposes
  Coordinators: CDC, FDA
- **$** Consider ways that results of periodic drug use surveys could be made available to food animal producers and veterinarians to encourage participation in data collection
  Coordinators: CDC, FDA, USDA
  Timeline for entire action item 6: Begin within one to two years

(7) Work with accrediting agencies to address antimicrobial drug-use monitoring as part of quality assurance in health care delivery systems. (Related Action Item: Prevention and Control #64)

Coordinators: CDC, HCFA
Timeline: Begin within one to two years

B. Issue: Implementation of the national plan for AR surveillance will require:

- **$** Reliable drug susceptibility data;
- **$** Adequate capacity and resources at state and local health and agricultural agencies; and
- **$** An accessible, centralized source of AR data.

1. Goal: Promote the consistent and appropriate use of reliable laboratory tests for antimicrobial drug susceptibility.

   a. Action Items

(8) Ensure that clinical laboratories that provide data for AR surveillance purposes have access to and routinely participate in pertinent training and proficiency testing programs with good performance and indicate AR testing methodologies in their surveillance reports (e.g., specific automated methods or manual techniques).

Coordinator: CDC; Collaborator: HCFA
Timeline: Initiated

(9) Evaluate the performance of licensed, automated AR testing devices in the context of changing resistance patterns and update their labeling where appropriate (e.g., changes in quantitative resistance that may make a test result invalid).

Coordinators: FDA, CDC
Timeline: Initiated

(10) Working with partners,[b] including the National Committee for Clinical Laboratory Standards (NCCLS), further develop, refine, and promote standardized clinical, epidemiologic, and laboratory methods for documenting and assessing the significance of drug resistance among yeasts and moulds, parasites, and viruses

Coordinators: CDC, NIH, FDA, USDA, HCFA
Timeline: Initiated

(11) Identify ways to overcome economic, legal, and other barriers to appropriate AR testing and to the reporting of results (e.g., sufficient human resources, cost considerations, empiric treatment recommendations, managed-care practices, etc.). (Related Action Item: Prevention and Control #34)

Coordinators: HCFA, HRSA, CDC, AHRQ
Timeline: Begin within one to two years

(12) Pursue legal mechanisms for manufacturers to provide otherwise unavailable drugs to government reference laboratories for the sole purpose of antimicrobial drug susceptibility testing (as part of surveillance) with the understanding that these drugs will not be used for drug discovery purposes.

Coordinator: CDC
Timeline: Begin within one to two years

2. Goal: Ensure that state and local health and agricultural agencies have the capacity to conduct surveillance of drug-resistant organisms of public health importance.

a. Action Items

(13) With state health and agriculture departments and other stakeholders, define needed core capacity (the minimum needed in human, laboratory, and

electronic resources) at the state and local level to ensure that basic AR surveillance is conducted in these jurisdictions. As part of this effort, ensure that state public health and veterinary diagnostic laboratories maintain the capacity to test the drug-susceptibility patterns of resistant organisms of public health importance, especially for drug-microorganism combinations for which testing methods are not routinely available at hospital and commercial laboratories.

Coordinators: CDC, USDA, FDA
Timeline: Begin within one to two years

(14) Provide resources to assist in meeting state and local core capacity needs for AR surveillance. Strive to provide consistent funding from year to year to state and local public health and veterinary diagnostic laboratories that meet quality assurance standards.

Coordinators: CDC, USDA
Timeline: Initiated

3. Goal: Disseminate surveillance data in a timely manner to public health officials, clinicians, and others who may make decisions based on an analysis of the data.

a. Action Items

(15) Provide an accessible, centralized source of AR data from major surveillance systems involving animal and human populations. In consultation with stakeholders, determine how to report AR data in a way that is valid and useful to interested parties (e.g., clinicians, public health officials, veterinarians, and researchers). Include sufficient detail in surveillance reports to permit local analysis and comparison with trends in drug use and medical and agricultural practices.

Coordinators: CDC, USDA, FDA, HCFA
Timeline: Begin within one to two years

(16) Provide health care system administrators and other decision makers with data on the impact of drug-resistant organisms (e.g., outcome, treatment costs) and on effective prevention and control measures.

Coordinators: CDC, AHRQ
Timeline: Begin within one to two years

C. Issue: Monitoring AR in agricultural settings is essential to ensure animal and plant health and a safe food supply.

1. Goal: Monitor AR in animal and plant pathogens and in bacteria that can be transmitted to humans through the food supply.

a. Action Items

(17) Expand and enhance coordination of surveillance for drug-resistance in enteric bacteria in sick and healthy humans and in sick and healthy animals on farms, at slaughter, and at retail. This effort includes:

- **$** Expanding the National Antimicrobial Resistance Monitoring System: Enteric Bacteria (NARMS:EB);
- **$** Comparing AR data on pathogenic and nonpathogenic organisms detected on farms (in sick and healthy animals), at slaughter, and in commercial food products; and
- **$** Utilizing these data to monitor the transmission of resistant infections and assess the effectiveness of prevention measures

Coordinators: CDC, FDA, USDA
Timeline: Initiated

(18) Evaluate the usefulness of monitoring sentinel human populations (e.g., farm, abattoir, fruit and vegetable, and food processing plant workers) and persons in the general community for infection or colonization with resistant enteric bacteria.

Coordinators: CDC, USDA, FDA
Timeline: Begin within three to five years

(19) Conduct pilot studies to assess the extent of environmental contamination by antimicrobial drug residues and drug-resistant organisms that enter the soil or water from human and animal waste. If contamination is detected, conduct appropriate surveillance in waste, surface and ground water, and soil from agricultural areas in which waste is used for fertilizer, and conduct studies to determine potential impact on human and animal health. (Related Action Item: Prevention and Control #55)

Coordinators: EPA, CDC, USDA
Timeline: Initiated

(20) Gather information on the relationship between antimicrobial pesticide and herbicide use and the emergence of drug-resistance by monitoring:

- **$** The prevalence and incidence of drug-resistant organisms in agricultural areas where antimicrobial pesticides are used and areas where they are not used, and
- **$** The prevalence of colonization or infection with resistant bacteria in human or animal populations who live or work near orchards or who consume fruit products sprayed (or treated) with antimicrobial pesticides. (Related Action Item: Prevention and Control #62)

Coordinators: EPA, CDC, USDA
Timeline: Begin within three to five years

II. Prevention and Control

Prevention and control of drug-resistant infections require measures to promote the appropriate use of antimicrobial drugs and prevent infection transmission. The concept of appropriate use may be expressed in various other ways, e.g., good antimicrobial stewardship or judicious, prudent, or rational use. In this *Action Plan*, appropriate antimicrobial drug use is defined as use that maximizes therapeutic impact while minimizing toxicity and the development of resistance. In practice, this means prescribing antimicrobial therapy when and only when beneficial to a patient; targeting therapy to the desired pathogens; and using the appropriate drug, dose, and duration. Appropriate antimicrobial drug use should not be interpreted simply as reduced use because these drugs offer valuable benefits when used appropriately. It is overuse and misuse that must be decreased to reduce the selective pressure favoring the spread of resistance.

Appropriate use can be facilitated in various ways, e.g., by promoting informed prescribing by clinicians, informing consumers about the proper use and limitations of antimicrobial drugs, and improving diagnostic techniques. The challenge facing public health organizations is to work with partners to identify effective methods of promoting appropriate antimicrobial drug use and to translate these interventions into routine medical practice.

Measures to prevent infection transmission, whether drug-resistant or not, are also very important in controlling AR. These measures include the appropriate use of vaccines and infection control, sanitation, hygiene measures, and other safe behaviors, e.g., safe sexual practices. Efforts to control drug-resistant infections must become part of everyday practice in health care settings across the nation, as well as in other settings (e.g., agriculture and veterinary medicine) in which antimicrobial drugs are used. Partners in many sectors of society and the general public will need to be involved in this effort.

A. Issue: Appropriate use of antimicrobial drugs can offer great benefits to patients, but overuse and misuse of these drugs can hasten the development of resistance and shorten the drug=s useful life.

1. Goal: Identify effective methods for promoting appropriate antimicrobial use.

a. Action Items

(21) Identify factors that promote or impede appropriate drug use in hospitals, extended care facilities, and outpatient settings in collaboration with partners.[b]
Coordinator: CDC; Collaborators: FDA, AHRQ, DVA, DoD
Timeline: Initiated

(22) Develop appropriate drug use policies and evaluate the impact (including on prescribing patterns, resistance rates, patient outcome, and cost) of implementing these policies in hospitals and other health care delivery settings. Identify ways to increase adherence to appropriate use policies proven to be beneficial in collaboration with partners.[b]

Coordinator: CDC; Collaborators: AHRQ, FDA, DVA, DoD, HCFA
Timeline: Initiated

(23) Evaluate the relationship between prescribing behavior and specific antimicrobial drug marketing and promotional practices. Assess the public health effects of these practices in collaboration with partners.[b]

Coordinators: CDC, FDA
Timeline: Begin within three to five years

(24) Help individual hospitals and health care systems analyze how the availability of AR data and computer-assisted decision support systems influences prescriber behavior, health outcomes, and costs. This plan may include the provision of computer software and the establishment of projects that involve the Medicare Peer Review Organizations (PROs).

Coordinator: CDC; Collaborators: HCFA, DVA, DoD
Timeline: Begin within three to five years

2. Goal: Promote appropriate antimicrobial use through educational and behavioral interventions found to be effective.

a. Action Items

(25) TOP PRIORITY ACTION ITEM - Conduct a public health education campaign to promote appropriate antimicrobial use as a national health priority. The campaign should involve many partners.[b] Elements of this campaign may include:

- **$** Culturally appropriate educational and behavioral interventions implemented through community-based programs that target patients and selected populations and communities, such as daycare centers and schools;
- **$** Strategies to improve patient adherence to appropriate therapies;
- **$** A clearinghouse for educational materials (e.g., booklets and CD-ROM presentations) on appropriate drug use and AR prevention;
- **$** A periodically updated priority list of drug-resistant microorganisms in humans and animals; and
- **$** A glossary disseminated through CDC Website that defines technical words commonly used in discussions of AR issues.

Coordinators: CDC, FDA; Collaborators: USDA, HCFA
Timeline: Begin within one to two years

(26) **TOP PRIORITY ACTION ITEM** - In collaboration with many partners,[b] develop and facilitate the implementation of educational and behavioral interventions that will assist clinicians in appropriate antimicrobial prescribing. Examples may include:

- **$** Educational curricula and training modules for all prescribing clinicians, health professions students, trainees, and senior health care administrators as part of quality assurance programs;
- **$** Clinical guidelines that address appropriate antimicrobial use;
- **$** Informatics technology (e.g., computer-assisted decision support) to assist in point-of-care prescribing and patient outcome monitoring;
- **$** Culturally appropriate materials and methods to help clinicians explain to patients the benefits and limitations of antimicrobial drugs and the importance of appropriate use of these drugs; and
- **$** Material that could be included in licensing, board certification, and credentialing examinations.

Coordinators: CDC, FDA; Collaborators: DoD, DVA, HRSA, HCFA
Timeline: Initiated

3. Goal: Promote appropriate antimicrobial use through regulatory changes and public policy actions.

a. Action Items

(27) Explore ways to integrate appropriate use information into antimicrobial package inserts and promotional materials, to provide such information to patients with each prescription, and to provide clear guidance to industry to ensure that promotion of antimicrobials directed towards consumers encourages appropriate use and discourages inappropriate use.

Coordinator: FDA; Collaborator: CDC
Timeline: Initiated

(28) Articulate factors that support the current approach of requiring prescription-only dispensing for all systemic (i.e., nontopical) antimicrobial drugs used in clinical medicine.

Coordinator: FDA; Collaborator: CDC
Timeline: Begin within one to two years

(29) Periodically review and update antimicrobial drug susceptibility information included in drug labeling, with input from stakeholders and other experts, e.g., the National Committee for Clinical Laboratory Standards (NCCLS) and CDC.

Coordinator: FDA
Timeline: Begin within one to two years

(30) Convene an advisory panel or other expert group involving stakeholders and

partners[b] to consider issues related to resistant pathogens that cause serious infections for which available treatment options are very limited or nonexistent. Issues include:

- **$** Criteria for designating such drug-pathogen combinations;
- **$** Compiling and updating a list of such drug-pathogen combinations;
- **$** Recommendations for diagnosis and management of patients with suspected or documented infection, including where appropriate that selected important drugs be preferentially used for the treatment of conditions associated with organisms that are resistant to other drugs;
- **$** Publicizing and facilitating access to clinical trials or compassionate use of investigational therapies;
- **$** Recommendations for preventing infection transmission;
- **$** Recommendations for performance and reporting of susceptibility test results for selected important drugs by clinical laboratories including possibly that they be reported to clinicians only on request if an organism is sensitive to other appropriate drugs;
- **$** Monitoring the use of selected important drugs, with consideration of changes in product labeling by FDA and in recommendations for use if increased resistance is detected; and
- **$** Labeling by FDA of selected important drugs with the recommendation that they be preferentially used for the treatment of conditions associated with organisms that are resistant to other drugs. (Related Action Item: This item will also be considered in conjunction with Product Development #80.)

  Coordinators: FDA, CDC
  Timeline: Begin within one to two years

(31) Convene a working group to examine the impact of federal reimbursement policies for home parenteral antimicrobial treatment, appropriate antimicrobial use, and appropriate use of antimicrobial susceptibility testing. Where needed, the working group will make recommendations for modifying these policies.
Coordinator: HCFA; Collaborators: CDC, HRSA
Timeline: Begin within one to two years

(32) Develop and submit measures for appropriate antimicrobial use to the National Committee for Quality Assurance for inclusion in Health Plan Employer Data and Information Set (HEDIS), which provides comparative data on managed care organizations.
Coordinator: CDC; Collaborator: HCFA
Timeline: Initiated

B. Issue: Improved diagnostic practices can enhance antimicrobial use and patient care.

1. Goal: Identify and promote the widespread use of diagnostic testing and reporting

strategies that effectively facilitate appropriate use of antimicrobial drugs in routine practice.

a. Action Items

(33) Evaluate the potential impact of improved diagnostic tests, including rapid point-of-care tests on antimicrobial drug use and patient care, and assess their financial implications. Take into account tests that distinguish between bacterial and viral infections, tests that identify resistant pathogens, and tests that distinguish common clinical entities such as bacterial sinusitis and acute bacterial otitis media from illnesses with similar manifestations for which antimicrobials are not beneficial. (Related Action Item: Research #76)
Coordinators: CDC, FDA, NIH; Collaborators: DVA, DoD
Timeline: Begin within one to two years

(34) Identify economic and other barriers in the health care system (e.g., reimbursement policies by third-party payers, managed care practices, cost considerations, empiric treatment recommendations, etc.) to diagnostic testing that promotes appropriate use of antimicrobials. Develop recommendations that remove disincentives or promote incentives to such testing.
Coordinator: HCFA; Collaborators: CDC, HRSA; AHRQ
Timeline: Begin within three to five years

(35) In collaboration with professional societies, industry, health departments, and other stakeholders and partners,[b] develop guidelines for clinicians and clinical microbiology laboratories that address:
- Appropriate specimen collection;
- Performance, interpretation, and reporting of antimicrobial (including antibacterial, antifungal, antiviral, and antiparasitic) susceptibility tests performed on clinical specimens; and
- Use of in-office (point-of-care) tests for infection, including AR infections.

Coordinator: CDC; Collaborators: FDA, DoD, DVA, HCFA, HRSA
Timeline: Begin within three to five years

(36) In collaboration with professional societies, industry, health departments, and other stakeholders and partners,[b] develop guidelines that address the use of clinical microbiology laboratories for use by health care delivery organizations. The guidelines will:
- Promote access to clinical microbiology services by clinicians;
- Promote access to appropriate on-site microbiology services in acute care facilities;
- Allow physicians to submit specimens to clinical laboratories other than those designated by their health care delivery organization or the patient=s insurance company, with appropriate justifications; and

$ Facilitate direct consultation between clinicians and laboratory personnel with appropriate expertise and authority.
Coordinator: CDC; Collaborator: HCFA for bullet 2.
Timeline: Begin within one to two years

(37) Promote the increased performance of direct examination of microbiological specimens (e.g., by Gram stain or other rapid method), in circumstances where appropriate, clinically relevant, and reliable information can be garnered, as a readily available point-of-care diagnostic test. This step will require working within the framework of the Clinical Laboratory Improvement Amendment (CLIA) regulations and involving medical education and health care delivery organizations.
Coordinator: CDC; Collaborator: HCFA
Timeline: Begin within one to two years

C. Issue: Preventing infection transmission through improved infection control, behaviors that prevent infection (e.g., safe sexual practices), and use of vaccines can help prevent the spread of antimicrobial resistance.

1. Goal: Identify ways to reduce disease transmission in health care settings and in the community.

a. Action Items

(38) Identify factors that promote transmission of drug-resistant pathogens in health care facilities, in extended care facilities, and in community settings including daycare centers and in the community at large. These may include characteristics of the facilities and of the populations that they serve.
Coordinator: CDC; Collaborators: DVA, DoD
Timeline: Initiated

(39) TOP PRIORITY ACTION ITEM - Evaluate the effectiveness (including cost-effectiveness) of current and novel infection-control practices for health care and extended care settings and in the community. Promote adherence to practices proven to be effective.
Coordinator: CDC; Collaborators: DoD, DVA, HCFA, HRSA
Timeline: Initiated

(40) Evaluate the cost-effectiveness and impact on patient care and drug resistance of medical devices that incorporate anti-infective compounds to prevent infection (e.g., anti-infective urinary catheters and prosthetic heart valves). Where appropriate (e.g., shown to be effective and not induce resistance), encourage the clinical use of these devices. (Related Action Item: Product Development #82)

Coordinator: CDC; Collaborators: AHRQ, DoD, DVA, FDA, HRSA, HCFA
Timeline: Begin within three to five years

(41) Encourage the development and implementation of clinical alternatives to those invasive medical procedures and devices that increase the risk of infection in hospitals and other health care settings, e.g., substitution of transcutaneous monitoring of blood oxygen levels of indwelling catheters.
Coordinator: CDC; Collaborators: FDA, DVA
Timeline: Begin within three to five years

(42) Evaluate the benefits and risks of incorporating antimicrobial, disinfectant, or antiseptic chemicals into consumer products (e.g., soap, toys, kitchen utensils, clothes, paints, plastics, and film preservatives) and of applying disinfectants and sanitizers to hard, non-porous surfaces such as food-contact surfaces, hospital premises, bathrooms, etc. Consider whether they have any efficacy in reducing infection and/or may play a role in promoting drug resistance.
Coordinators: CDC, EPA; Collaborator: FDA
Timeline; Initiated

2. Goal: Promote infection control through behavioral and educational interventions.

a. Action Items

(43) Conduct a public health campaign to promote hand hygiene and other hygienic practices, as well as other behaviors that prevent the transmission of infectious organisms, in collaboration with professional societies and stakeholders. This campaign may be coordinated with the public health education strategy to promote appropriate antimicrobial use described in Action Item #25: Prevention and Control. Components will include developing, evaluating, and facilitating the implementation of school-based and other programs that
promote hand hygiene and other behaviors that prevent infection, building on previous campaigns (e.g., American Society of Microbiology=s Operation Clean Hands).[27]
Coordinator: CDC
Timeline: Begin within one to two years

(44) Facilitate and support the activities of infection control programs in health care settings as a component of medical care. Promote infection control education at all stages of training and practice for all health care workers who have contact with patients.
Coordinator: CDC; Collaborators: DVA, HCFA, DoD, HRSA
Timeline: Initiated

(45) Support ongoing public health education campaigns on food safety, such as FDA and USDA=s Fight Bac program,[28] whose aims are to educate food producers, suppliers, retailers, and consumers about food safety practices that reduce foodborne infections (including AR infections).[29]

Coordinators: USDA, CDC, FDA
Timeline: Initiated

(46) Educate the public about the merits and safety of irradiation as one tool to reduce bacterial contamination of food.

Coordinator: CDC
Timeline: Begin within one to two years

3. Goal: Optimize the use of vaccines to prevent drug-resistant infections and reduce antibiotic use.

a. Action Items

(47) Support community-based programs that promote and facilitate availability of recommended vaccinations for adults and children.

Coordinator: CDC
Timeline: Initiated

(48) Identify vaccines useful in preventing drug-resistant infections and reducing antimicrobial drug use, and evaluate novel methods for improving coverage with these vaccines. For example:

- **$** Evaluate the risks and benefits of allowing certain vaccines for adults (e.g., for pneumococci and influenza virus) to be dispensed by pharmacists without prescription and
- **$** Review and evaluate methods to promote administration of pneumococcal vaccines (e.g., offering vaccination when patients are discharged from the hospital), and encourage the use of methods found to be effective.

Coordinator: CDC; Collaborators: DVA, FDA, HCFA
Timeline: Begin within three to five years

D. Issue: Prevention and control of drug resistance in agriculture and veterinary medicine is important to promoting animal and plant health, as well as in preventing AR transmission to humans through the food supply or through contact with infected animals or the environment.

1. Goal: Improve understanding of the risks and benefits of antimicrobial use, and ways to prevent the emergence and spread of drug resistance, in agricultural and veterinary settings.

a. Action Items

(49) Evaluate the nature and magnitude of the impact of using various antimicrobial drugs as growth promotants in different species, using current animal husbandry practices. Use this information to assist in risk-benefit assessments of such use.

Coordinator: USDA; Collaborators: CDC, FDA
Timeline: Begin within one to two years

(50) Conduct additional research to further define the effects of using various veterinary drugs on the emergence of resistant bacteria that infect or colonize food animals of different species, using various animal husbandry practices. Identify risk factors and preventive measures. Assess the associated risk of:

- **$** Transmission of AR infections to humans;
- **$** Clinical disease in humans; and
- **$** Transfer of resistance factors from animal flora to human flora.

Coordinators: CDC, USDA, FDA
Timeline: Initiated

(51) Conduct epidemiologic and laboratory studies to assess the risk of development and transfer of resistance related to the use of antimicrobial drugs in food and nonfood plants, and identify risk factors and potential preventive measures.

Coordinator: USDA; Collaborators: CDC, FDA, EPA
Timeline: Initiated

(52) Develop rapid tests for inspecting fresh commodities like fruit for evidence of contamination with bacteria that are resistant to antibiotics.

Coordinator: USDA; Collaborators: EPA, FDA, CDC
Timeline: Begin within one to two years

(53) Evaluate the effect of current food processing and distribution methods on the emergence and spread of drug-resistant organisms.

Coordinator: USDA; Collaborators: CDC, FDA
Timeline: Begin within one to two years

(54) Identify and evaluate new food pasteurization strategies.

Coordinator: USDA; Collaborators: FDA, CDC
Timeline: Begin within three to five years

(55) Assess the risk of AR emergence and spread due to environmental contamination by antimicrobial drugs or by resistant bacteria in animal and human waste. Collect information on whether environmental contamination by antimicrobial drugs can lead to the development of resistance in bacteria that live in the soil or in water. (Related Action Item: Surveillance #19)

Coordinators: USDA, CDC, EPA, FDA
Timeline: Initiated

(56) Assess the impact of antimicrobial use in companion animals (pets) on colonization and infection with drug-resistant organisms in the animals and their human household contacts.
Coordinator: CDC
Timeline: Begin within three to five years

2. Goal: Promote appropriate antimicrobial use in agricultural and veterinary settings.

a. Action Items

(57) Work with veterinary and agricultural communities to help educate users of veterinary and agricultural antimicrobials about AR issues, and promote the implementation and evaluation of guidelines that address these issues:
- **$** Appropriate antimicrobial use in agricultural and veterinary settings;
- **$** Performance and interpretation of antimicrobial susceptibility tests performed on specimens from different species of animals; and
- **$** Point-of-care tests for infection, including AR infections.

Coordinators: USDA, CDC, FDA; Collaborator: EPA
Timeline: Initiated

(58) TOP PRIORITY ACTION ITEM - In consultation with stakeholders, refine and implement the proposed FDA framework[30] for approving new antimicrobial drugs for use in food-animal production and, when appropriate, for re-evaluating currently approved veterinary antimicrobial drugs. The proposed framework includes the following major steps:
- **$** Categorize antimicrobial drugs according to their importance in human medicine.
Timeline: Initiated
- **$** Develop an approach to the establishment of thresholds for drug resistance in selected pathogens.
Timeline: Initiated
- **$** Revise requirements for the industry=s submission of drug use data.
Timeline: Initiated
- **$** Develop procedures to assess microbial safety of antimicrobial drug use in food-producing animals.
Timeline: Initiated

In support of the concepts articulated in the framework document:
- **$** Conduct risk assessments on the human health impact of using selected antimicrobials important in human medicine in food-producing animals
Timeline: Initiated
- **$** Initiate appropriate steps to address any unacceptable human health impact, if identified by the risk assessments, for drugs categorized as being of critical importance in human medicine
Timeline: Begin within one to two years
Coordinator: FDA

(59) Strongly encourage involvement of veterinarians in decisions regarding the use of systemic antimicrobial drugs in animals, regardless of the distribution system through which the drug is obtained (e.g., regardless of whether a prescription is required to obtain the drug).

Coordinators: FDA, USDA
Timeline: Initiated

(60) Evaluate the potential impact of making all systemic veterinary antimicrobial drugs available by prescription only.

Coordinators: FDA, USDA
Timeline: Begin within three to five years

(61) Convene an expert group to consider how to incorporate AR issues into regulations governing the registration and use of antimicrobials and antibiotic pesticides. Invite external experts, stakeholders, and the public to provide input.

Coordinator: EPA
Timeline: Begin within one or two years

E. Issue: Efforts to prevent and control AR emergence and spread must be comprehensive and multifaceted, involve a wide variety of nonfederal partners and the public, and become a part of routine practice nationwide.

1. Goal: Ensure input from nonfederal experts on federal efforts to combat antimicrobial resistance.

a. Action Item

(62) Establish an ongoing mechanism to obtain periodic input from external experts on AR issues. This process will include ensuring input from stakeholders and partners[b] (e.g., state and local health agencies, the private sector, and the public) in developing and reviewing federal efforts to address antimicrobial resistance.

Coordinators: CDC, FDA, NIH; Collaborators: USDA, EPA, DoD, DVA, AHRQ, HRSA, HCFA
Timeline: Begin within one to two years

2. Goal: Develop and evaluate comprehensive demonstration programs to prevent and control AR.

a. Action Item

(63) **TOP PRIORITY ACTION ITEM** - Support demonstration projects to evaluate comprehensive strategies that use multiple interventions to promote appropriate drug use and reduce infection rates. These projects will include the following steps:

- **$** Assess how interventions found effective in research studies can be applied routinely and most cost-effectively on a large scale;
- **$** Evaluate the use of these programs in health care systems (federal and nonfederal), in the community, and in agricultural and veterinary settings; and
- **$** Involve partnerships with local and state agencies, health care systems, professional societies, community organizations, schools, private industry, and the public.

Coordinator: CDC; Collaborators: FDA, DVA, DoD, HRSA, HCFA, USDA
Timeline: Initiated

3. Goal: Incorporate into routine clinical practice AR prevention strategies and programs that have been found to be beneficial in research and demonstration projects.

a. Action Items

(64) Utilize federal health care systems (e.g., DoD, DVA) as models for AR surveillance and prevention and control activities involving appropriate drug use, optimized diagnostic testing, infection control, and vaccination practice.
Coordinators: CDC, DVA, DoD, HCFA, HRSA
Timeline: Begin within three to five years

(65) For all health care systems for which federal funds are provided, identify and promote strategies to establish AR prevention and control activities as part of quality monitoring programs.
Coordinators: CDC, DVA, DoD, HCFA, HRSA
Timeline: Initiated

(66) Encourage nationally recognized accrediting agencies such as the National Committee for Quality Assurance (NCQA) and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) to include accreditation standards that promote efforts to prevent and control AR, including appropriate antimicrobial use, infection control, vaccine use, and diagnostic testing. These standards may draw on the findings of existing data and demonstration programs and AHRQ Evidence-Based Practice Centers.
Coordinator: CDC; Collaborators: HCFA, AHRQ
Timeline: Begin within one to two years

III. Research

Antimicrobial resistance is among the most challenging problems in microbiology, clinical medicine, and public health. Antimicrobial resistance is not one problem, but an overarching term for an array of problems inherent in the evolution of microbes and influenced by antimicrobial use. Basic and clinical research provides the fundamental knowledge necessary to develop appropriate responses to antimicrobial resistance emerging and spreading in hospitals, communities, farms, and the food supply. Major scientific accomplishments throughout the years have contributed much to the understanding of the fundamental biological processes of AR within microbes and the resulting impact on humans, animals, and the environment. This knowledge base provides us the opportunity to influence these processes and outcomes.

Because of its broad scope, the U.S. research community has a major contribution to make in meeting the goals the AR Task Force has set forth. The research and development of diagnostic tests, new antimicrobial agents, novel therapeutic products, and vaccines and other preventive approaches in response to AR is a multistep process that begins with basic research discoveries and ends with the availability and use of a new product or implementation of a process. Along this pathway three areas need to be addressed: the identification of gaps and needs in the molecular and cellular understanding of resistance, the infrastructure to support a robust research community, and a means for moving research findings into the development of new products.

The Interagency Task Force has worked with representatives from the public and private sector to identify important research needs in microbial physiology, ecology, genetics and mechanisms of resistance. Existing gaps in knowledge and understanding should be addressed to augment the federal and private sector response to the overall problem. Efforts are underway to build and enhance the field of AR research, through increased focus, recognition, and collaboration. The aim is to develop a research infrastructure to support a critical mass of AR researchers who will interact, exchange information, and stimulate new discoveries. In order to move novel ideas arising in the research laboratory to useful products or approaches, support of the underlying infrastructure to study and test products and a mechanism to transition to industrial partners is necessary.

This effort will involve federal agencies that conduct, support and promote basic and clinical research in academia and industry and will involve prioritizing needs, identifying key opportunities, recruiting new investigators to the field, and making responsible use of resources to address AR problems.

A. Issue: Specific scientific gaps remain in the understanding of microbial physiology, ecology, genetics and mechanisms of resistance.

1. Goal: Identify gaps and address existing research needs and identify new ones.

a. Action Items

(67) Additional research, including high risk and high payoff research in nontraditional fields, is needed to enhance the understanding and assess the impact of:

- Mechanisms of AR emergence, acquisition, spread, persistence, and decline, with special regard to multidrug resistant organisms;
- Emergence and transfer of resistance genes among microorganisms in vivo, including epidemiologic factors;
- Microbial ecology and the role of normal flora as a repository of resistance factors, as well as the use of susceptible bacterial populations in the control of antimicrobial resistance;
- Effects of preventive, therapeutic, growth-promoting agents and residues of agents in the environment on the microbiota of animals, plants, soil, and aquatic environments;
- Host factors and immune modulators (e.g., cytokines) in clinical resistance to treatments for opportunistic infections;
- The determinants of colonization and infection with drug-resistant pathogens; and
- Variations in antimicrobial use patterns that may affect the emergence and spread of resistance and the outcome of treatment, such as:
  - Differences in duration and dosage in the administration of antimicrobial agents;
  - Prophylactic use of antimicrobial (including antibacterial and antifungal) agents;
  - Drug combinations used to treat resistant organisms; and
  - The rotation (cycling) of antimicrobial drugs and other similar changes in selection and use of drug classes.

Coordinator: NIH; Collaborators: CDC, FDA, DVA, USDA, EPA, DoD
Timeline: Initiated

(68) Conduct further government-wide assessments with external input on the scope and composition of AR research to identify research opportunities.
Coordinators: NIH, CDC, FDA, USDA; Collaborators: DoD, DVA, AHRQ, EPA, HCFA
Timeline: Initiated

B. Issue: The existing research infrastructure needs to ensure a critical mass of researchers in AR and related fields.

1. Goal: Augment the scientific research infrastructure.

a. Action Items

(69) Work with the appropriate peer review structures to ensure that the requisite expertise is applied to the review process to facilitate funding of quality AR research.

Coordinators: NIH, DVA, FDA
Timeline: Begin in one to two years

(70) TOP PRIORITY ACTION ITEM - Provide to the research community genomics and other powerful technologies to identify targets in critical areas for the development of new rapid diagnostics methodologies, novel therapeutics, and interventions to prevent the emergence and spread of resistant pathogens. Examples include tools such as microbial genome sequences, information on comparative genomics, DNA chip technology, informatics, and assistance in the application and use of these tools.
Coordinator: NIH; Collaborators: DoD, USDA, FDA
Timeline: Initiated

(71) Encourage sharing of AR data between industry and the research community, including genomics and other technologies.
Coordinator: NIH; Collaborators: DoD, USDA, FDA
Timeline: Begin in three to five years

2. Goal: Develop a critical mass of researchers in AR.

a. Action Items

(72) Bring new researchers into the field, by utilizing appropriate strategies such as training and research opportunities.
Coordinator: NIH; Collaborators: CDC, FDA, USDA, DoD, DVA
Timeline: Initiated

(73) Organize conferences that address research issues relating to AR.
Coordinator: NIH; Collaborators: CDC, USDA, FDA, DVA, DoD, AHRQ
Timeline: Initiated

C. Issue: Special efforts are needed to translate research findings into medically useful products for human and agricultural/veterinary use, such as novel antimicrobial therapeutics, diagnostic tests, vaccines and other tools for preventing AR emergence and spread.

1. Goal: Address the governmental role in translating novel ideas into new clinically relevant products, focusing on gaps not filled by pharmaceutical industry and other nongovernment groups.

a. Action Items

(74) Explore the need to encourage preclinical studies on the toxicology, pharmacokinetics, and pharmacodynamics of novel therapeutic agents for the

treatment of multidrug-resistant pathogens and facilitate the transition of potential products from preclinical to clinical studies leading to development by industry of novel therapeutic agents.

Coordinator: NIH; Collaborators: DoD, DVA, FDA, USDA
Timeline: Begin within one to two years

(75) **TOP PRIORITY ACTION ITEM** - In consultation with academia and the private sector, identify and conduct human clinical studies addressing AR issues of public health significance that are unlikely to be studied in the private sector, such as:

- **$** Novel therapies;
- **$** Existing antimicrobials administered in treatment regimens and combinations that may not be included in approved indications and dosing schedules; and
- **$** Other products and practices relevant to the control and treatment of antimicrobial-resistant pathogens including devices, diagnostics, antimicrobial soaps, disinfectants, etc.

Coordinator: NIH; Collaborators: CDC, DVA, DoD, FDA
Timeline: Begin within one to two years

2. Goal: Develop rapid, inexpensive, point-of-care diagnostic methods to facilitate appropriate use of antimicrobials.

a. Action Item

(76) **TOP PRIORITY ACTION ITEM** - Identify, develop, test, and evaluate new rapid diagnostic methods for human and veterinary uses with partners including academia and the private sector. Such methods should be accurate, affordable, and easily implemented in routine clinical settings and may include:

- **$** Tests for resistance genes that are associated with drug resistance, including nonculture specimens;
- **$** Rapid point-of-care diagnostics for patients with viral respiratory infections and clinical syndromes such as otitis media, sinusitis, and pneumonia; and
- **$** Rapid methods for detecting drug resistance among fungi, parasites, viruses, and mycobacteria.

Coordinators: NIH, FDA; Collaborators: DoD, USDA, CDC, AHRQ, DVA
Timeline: Initiated

3. Goal: Develop new products and strategies to prevent and treat colonization and infection with resistant organisms in patients, prevent transmission of resistant infections in the community, and prevent AR emergence

a. Action Items

(77) **TOP PRIORITY ACTION ITEM** - Encourage basic and clinical research in support of the development and appropriate use of vaccines in human and veterinary medicine in partnership with academia and the private sector. Vaccines are needed to:

- **$** Prevent viral infections that predispose patients to and are difficult to differentiate from bacterial infection and are presumptively treated with antibacterial agents (e.g., influenza virus);
- **$** Prevent colonization, infection, and transmission of resistant organisms such as enterococci and staphylococci; and
- **$** Prevent common bacterial infections (such as *S. pneumoniae,* nontypable *Haemophilus influenzae)* to reduce antibacterial use.

Coordinators: NIH, FDA; Collaborators: CDC, DoD, DVA, USDA
Timeline: Initiated

(78) Encourage basic and clinical research in support of novel approaches to preventing or treating infections with resistant organisms that occur in humans and animals by partnering with academia and the private sector. Novel approaches may include:

- **$** Bacteriophage therapy;
- **$** Active (vaccine) and passive (antibody, hyperimmune globulin) immunization;
- **$** Host-derived antimicrobial agents;
- **$** Nonantibiotic antimicrobials and nonchemical approaches with broad or nonspecific anti-infective activities (e.g., defending and nonspecific immunostimulants, such as defensins, ribozymes, etc.); and
- **$** Microbial ecology (probiotics, direct fed microbials, etc.).

Coordinator: NIH; Collaborators: DoD, DVA, FDA, USDA, CDC
Timeline: Initiated

IV. Product Development

New products are not being developed rapidly enough to address increasing microbial resistance. Needed products include not only new classes of antimicrobials able to kill otherwise resistant organisms, but also vaccines and anti-infective devices with the potential to prevent infections as well as improved diagnostic tools to aid in appropriate use of therapeutics. With respect to antimicrobial drugs, each new agent represents a major investment by a pharmaceutical company, which must shepherd the product through pre-clinical studies and clinical testing, followed by large and expensive clinical trials. Pharmaceutical companies may be reluctant to invest extensive resources in the development of drugs, such as those antimicrobials targeted to resistant organisms, which are often given for short time periods to small numbers of patients. Manufacturers are similarly concerned that appropriate use policies may limit sales and profits. On the other hand, when a drug is used widely, allowing recovery of costs and profitability, resistance may develop more rapidly and shorten the useful life of the drug.

Due to these economic realities **B** as well as to scientific limitations and a lag in the perception of a need for new agents **B** very few novel antimicrobial drugs have reached the market for several years. A major aim of this interagency effort is to work with the private sector to explore and test innovative ways to address these issues. Approaches to be considered include providing incentives (and overcoming disincentives) to promote and assist the development of important products to address AR.

Product development is also a very important issue for veterinary medicine and agriculture. U.S. agencies and private sector partners must intensify efforts to encourage the development and use of veterinary drugs and agricultural practices that are unlikely to stimulate resistance to important human drugs or spread resistant pathogens to humans. Again, increased attention also needs to be turned to strategies to prevent infections of animals (e.g., vaccines, changes in husbandry) and to the improved use of existing and new products.

A. Issue: Researchers and drug manufacturers need to be better informed of current and projected gaps in the arsenal of antimicrobial drugs, vaccines, and diagnostics and of potential markets for these products.

1. Goal: Provide a systematic assessment of the current status and projected future needs for AR products.

a. Action Item

(79) TOP PRIORITY ACTION ITEM - Create an Interagency AR Product Development Working Group to identify and publicize priority public health needs in human and animal medicine for new AR products (e.g., innovative drugs, targeted spectrum antibiotics, point-of-care diagnostics, vaccines and other biologics, anti-infective medical devices, and disinfectants). The Working Group will take these steps:

- **$** Obtain input from stakeholders, including pharmaceutical companies, physicians, epidemiologists, and microbiologists, on which products are needed;
- **$** Involve experts in the nonmedical disciplines (e.g., engineering and remote sensing, etc.);
- **$** Model future resistance trends, product needs, and potential markets (particularly for novel and narrow spectrum uses), taking into account AR surveillance data and numbers of patients at high risk of developing drug resistant infections (e.g., increases in immunocompromised patients);
- **$** Evaluate current market incentives for the development of priority AR products (Related Action Item: Product Development #80);
- **$** Reassess AR product priorities on a regular basis;
- **$** Evaluate the availability of currently approved, critical products where shortages or potential for shortages exists and develop an approach to ensure that the supply of such products is adequate to meet public health needs; and
- **$** Communicate the information and priorities developed by the Workgroup to inform and allow coordination with planning and action efforts in research, prevention and control, and product development.
  Coordinators: FDA, USDA, CDC; Collaborators: NIH, AHRQ
  Timeline: Begin within one to two years

B. Issue: Existing market incentives and regulatory processes may be insufficient to stimulate the development of certain priority AR products while fostering their appropriate use.

1. Goal: Investigate and act upon potential approaches for stimulating and speeding the entire AR product development process, from drug discovery through licensing.

a. Action Items

(80) **TOP PRIORITY ACTION ITEM** - Identify ways (e.g., financial and/or other incentives or investments) to promote the development and/or appropriate use of priority AR products, such as novel compounds and approaches, for human and veterinary medicine for which market incentives are inadequate.

- **$** This process should include consultation with outside stakeholders, economic consultants, and the AR Product Development Working Group (Related Action Item: Product Development #79).
- **$** All such proposals will require careful economic modeling and analysis. New approaches should be used on a trial basis for appropriate time periods and the costs and benefits of incentives used in these pilot programs should be monitored to assess the return on the public investment.

- **$** Similar incentives should be explored for ensuring adequate availability of existing products that meet critical public health needs but for which market incentives are inadequate to assure supply. (Related Action Item: Product Development #79).
  Coordinators: FDA, CDC; Collaborators: USDA, AHRQ
  Timeline: Begin within one to two years

(81) Consider, in consultation with academia and industry, whether government has a constructive role to play in discovery of drugs and other products targeted to address areas where market incentives are limited and unmet needs exist (e.g., novel antimicrobial drugs targeted to specific resistant organisms). (Related Action Items: Research Issue B)

- **$** Such a role could utilize intramural, extramural or partnership type mechanisms. Products developed under such mechanisms could be licensed commercially either with or without specific stipulations regarding use.
  Coordinator: NIH; Collaborators: USDA, FDA, CDC
  Timeline: Begin within three to five years

(82) Continue ongoing approaches that streamline the regulatory process, including clinical trials and enhanced pre-clinical studies (e.g., use of pharmacokinetics, and pharmacodynamics data) to help bring AR products (including drugs, vaccines, diagnostics and devices) to market as efficiently and rapidly as possible, while still assuring their safety and efficacy.

- **$** This approach might involve use of an expedited process in which certain drugs are considered for approval, in accordance with Subpart E of the Investigational New Drug (IND) regulations. It might also involve defining new surrogate endpoints that indicate a meaningful response benefit over existing treatments for particular infections (e.g., HIV-1 RNA viral loads or CD4 counts as surrogate markers in the treatment of HIV/AIDS), in accordance with Subpart H of New Drug Application (NDA) regulations.
- **$** In the case of approvals for anti-infective medical devices, AR concerns will be addressed during the pre-and post-licensing review, to ensure that these products reduce infection without engendering significant resistance.
- **$** For products specifically targeted to serious or life-threatening AR infections, for which there are few therapeutic alternatives, develop approaches for more focused development programs that would streamline product availability. This should be done in consultation with all of the stakeholders in the process.
  Coordinator: FDA; Collaborator: USDA
  Timeline: Initiated

C. Issue: The development and use of antimicrobial drugs and related products in agriculture and veterinary medicine should be optimized to reduce the development and transfer of resistance to pathogens that can infect humans.

1. Goal: Promote the development and use of new and existing AR products that reduce the risk of the development and transfer of antimicrobial resistance to humans, as well as new approaches to reducing agricultural and veterinary use of antimicrobial drugs.

   a. Action Items

   (83) In consultation with stakeholders and expert consultants, identify ways to promote the development of new and alternative veterinary treatments and the improved use of existing therapies that are unlikely to stimulate resistance to drugs in human medicine. This action will include consideration of the incentives and approaches listed in Action Items #80 (Product Development), #28 (Prevention and Control), and #78 (Research) and the implementation of pilot programs to stimulate the development of priority products that meet critical animal health needs.

   $ Approaches for evaluation should include ways to improve and/or reduce the use of specific antimicrobial drugs, as well as ways to prevent infection, such as vaccines, changes in animal husbandry, and the use of competitive exclusion products (e.g., treatments that affect the intestinal flora of food animals).

   Coordinators: FDA, USDA, NIH, CDC
   Timeline: Begin within three to five years

   (84) Streamline the regulatory and approval process for veterinary antimicrobial drugs and related products that are unlikely, now or in the future, to result in transfer of antimicrobial resistance to humans.

   Coordinators: FDA, USDA
   Timeline: Begin within three to five years

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