



REPORT TO THE PRESIDENT ON COMBATING ANTIBIOTIC RESISTANCE

Executive Office of the President
President's Council of Advisors on
Science and Technology

September 2014





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President Barack Obama
The White House
Washington, DC 20502

Dear Mr. President:

We are pleased to send you this report, *Combating Antibiotic Resistance*, prepared at your request by your Council of Advisors on Science and Technology (PCAST). This report offers practical recommendations to the Federal government for strengthening the Nation's ability to combat the rise in antibiotic-resistant bacteria. PCAST finds that without rapid and coordinated action, the Nation risks losing the tremendous public health progress made over the last century from the discovery and development of antibiotic drugs, thereby threatening patient care, economic growth, public health, agriculture, economic security, and national security.

PCAST's recommendations were developed in consultation with a working group of experts in antibiotic resistance who span the human and veterinary health sectors, including scientists, clinicians, epidemiologists, regulators, and economists, as well as representatives from the pharmaceutical industry, biotechnology companies, and agribusiness. Based on these discussions, PCAST identified several areas that require urgent attention and outlined a set of practical and actionable steps that the United States government should take over the next few years to bring the antibiotic-resistance crisis under control. Those steps focus on ways to improve our surveillance capabilities for resistant bacteria, increase the longevity of current antibiotics, and accelerate the rate at which new antibiotics and other interventions are discovered and developed.

In the fight against microbes, no permanent victory is possible: as new treatments are developed, organisms will evolve new ways to become resistant. This reality underscores how essential it is to embark now on a course of action that will ensure an effective arsenal of antibiotics that is continually renewed. By taking the recommended steps, the United States and global community can continue to reap the benefits of these essential medicines. PCAST is grateful for the opportunity to provide these recommendations to you and stands ready to provide whatever further assistance we can on this critical issue.

Sincerely,



John P. Holdren
Co-chair, PCAST



Eric S. Lander
Co-chair, PCAST



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Executive Summary

Introduction

For an American in the 21st century, it is hard to imagine the world before antibiotics. At the beginning of the 20th century, as many as nine women out of every 1,000 who gave birth died, 40 percent from sepsis. In some cities as many as 30 percent of children died before their first birthday. One of every nine people who developed a serious skin infection died, even from something as simple as a scrape or an insect bite. Pneumonia killed 30 percent of those who contracted it; meningitis killed 70 percent. Ear infections caused deafness; sore throats were not infrequently followed by rheumatic fever and heart failure. Surgical procedures were associated with high morbidity and mortality due to infection.

This picture changed dramatically with three major developments: improvements in public health, vaccines, and antibiotics. Over the course of the 20th century, deaths from infectious diseases declined markedly and contributed to a substantial increase in life expectancy. Antibiotics, in particular, have saved millions of lives.

But, the United States and the world are now at dire risk of losing this progress. Bacteria and other microbes evolve in response to their environment and inevitably develop mechanisms to resist being killed by antibiotics. For many decades, the problem was manageable as the growth of resistance was slow and the pharmaceutical industry continued to create new antibiotics.

Over the past decade, however, this brewing problem has become a crisis. The evolution of antibiotic resistance is now occurring at an alarming rate and is outpacing the development of new countermeasures capable of thwarting infections in humans. This situation threatens patient care, economic growth, public health, agriculture, economic security, and national security.

In November 2013, President Obama tasked his President's Council of Advisors on Science and Technology (PCAST) with making practical and actionable recommendations concerning how the Federal Government can best combat the rise of antibiotic resistance that is threatening the health of Americans and people around the world. To respond to this request, PCAST rapidly assembled a taskforce of 15 non-Federal experts in the field of antibiotic resistance and also consulted with experts across Federal agencies. Informed by extensive discussions with these experts, PCAST developed this report.

In this report, PCAST recommends a set of practical and actionable steps that the United States government should take over the next few years to bring the antibiotic-resistance crisis under control, through focused efforts in three areas:

- (1) **improving our surveillance of the rise of antibiotic-resistant bacteria** to enable effective response, stop outbreaks, and limit the spread of antibiotic-resistant organisms, and acting on surveillance data to implement appropriate infection control;
- (2) **increasing the longevity of current antibiotics**, by improving the appropriate use of existing antibiotics, preventing the spread of antibiotic-resistant bacteria and scaling up proven interventions to decrease the rate at which microbes develop resistance to current antibiotics;
- (3) **increasing the rate at which new antibiotics, as well as other interventions, are discovered and developed.**

Background

The Centers for Disease Control and Prevention (CDC) estimates that the annual impact of antibiotic-resistant infections on the U.S. economy is \$20-35 billion in excess direct health care costs, with additional costs to society for lost productivity as high as \$35 billion per year and 8 million additional days in hospitals. And the problem is worsening. A number of bacterial diseases are almost or entirely untreatable because the causal agents have acquired resistance to all of the antibiotics that can be deployed against them. Resistance is due largely to extensive exposure of bacteria to antibiotics. Antibiotics impose a selection pressure for resistant bacteria – that is, susceptible bacteria die in the presence of the antibiotic, whereas resistant strains survive and then multiply without competition from the susceptible strains.

Addressing the growing crisis in antibiotic resistance will require attention to several areas:

- **Human Health Care.** Antibiotics are among the most commonly prescribed drugs used in human medicine. CDC estimates, however, that up to 50 percent of all the antibiotics prescribed for patients in the United States are not needed or are not optimally prescribed. Reasons for antibiotic overuse in health care include lack of rapid, accurate and well-validated point-of-care diagnostic tests and pressure from the patient (or the patient's family) due to insufficient understanding of antibiotic use. This misuse and overuse of antibiotics in human medicine, both in the United States and internationally, is a major contributor to rising antibiotic resistance.
- **Animal Agriculture.** Medically important antibiotics are also extensively used in animal agriculture not only to treat sick animals, but also to promote animal growth and to prevent infections. All of these uses promote the development of antibiotic resistance among bacteria in animals, and these resistant strains do, at least in some cases, spread to humans. While the extent to which antibiotic resistance in animal agriculture contributes to human infections is not known, the risks to human health posed by the agricultural use of antibiotics are, appropriately, a matter of very serious concern.
- **Drug Development.** The world lacks a robust pipeline of new antibiotics to replace those being steadily lost to antibiotic resistance. The number of new systemic antibacterial

agents approved by the Food and Drug Administration (FDA) each year has decreased steadily over the past three decades. The drug development pipeline is failing for a variety of reasons – including scientific challenges in discovering and developing new drugs; practical challenges in conducting the clinical trials needed for new-drug approval; and low economic returns that have made the development of new antibiotics an unattractive investment. As a result, large pharmaceutical companies have decreased or eliminated their investments in antibiotic drug development.

- **Surveillance and Response.** Situational awareness is crucial for addressing national and international threats. Yet, the United States currently lacks comprehensive monitoring for antibiotic resistance emerging domestically and being imported from abroad. Our surveillance systems are woefully underfunded. Powerful tools that emerged from the Human Genome Project have the ability to reveal how antibiotic resistance arises and spreads across health care facilities, agriculture, the environment and international borders, but they are not being routinely used. And adequate public and animal health infrastructure for monitoring antibiotic use and resistance is lacking in many states and localities.

The Way Forward

Federal spending for the antibiotic crisis has been limited – approximately \$450 million in direct funding in FY14, corresponding to just over \$1.40 per American. Funds are allocated across the Department of Health and Human Services (HHS), Department of Veterans Affairs (VA), Department of Defense (DoD), and Department of Agriculture (USDA). About 75% is used for basic and applied research, with the rest directed toward stewardship and surveillance in human health care and agricultural programs.

This funding is dwarfed by the annual impact on the United States, including 23,000 deaths and \$55-70 billion per year in economic impact. The right investment of Federal resources could reduce the economic losses. For example, a 30 percent reduction in impact would save approximately \$20 billion per year, including reducing Medicare expenditures.

Fortifying the United States against antibiotic resistance will require new Federal investments. Supporting increased surveillance, stewardship, research and clinical development will require an additional \$450 million per year – that is, doubling the current investment from \$450 million to \$900 million. Incentivizing commercial development of new antibiotics, through partnerships with industry, will require an additional investment of \$800 million per year to yield approximately one new antibiotic per year. Such aggressive action and investments in the antibiotic crisis are justified to contain the public health and economic impacts, which are likely to increase even more rapidly in the future if not checked.

Recommendations

PCAST recommends specific actions and investments intended to achieve better surveillance, stewardship of currently used antibiotics, and development of new antibiotics. These investments must be wisely spent, which necessitates examining and improving upon past efforts. Here, we summarize the recommendations that PCAST makes in its full report.

Recommendation 1. Ensure Strong Federal Leadership

Stronger Federal coordination and oversight of efforts to combat antibiotic resistance is essential. The President should task the National Security Council, in coordination with the Office of Science and Technology Policy and the Office of Management and Budget (OMB), with oversight and coordination of Federal efforts to combat antibiotic resistance, and appoint a member of the National Security Council staff as White House Director for National Antibiotic Resistance Policy (DNARP), supported by adequate professional staff, devoted fully to ensuring integration and accountability and annual reporting. The President should also establish an interagency Task Force on Combating Antibiotic-Resistant Bacteria (TF-CARB) co-chaired by the Secretaries of Agriculture, Defense, and Health and Human Services or their designated deputies and having members from all relevant agencies and establish a President's Advisory Council on Combating Antibiotic-Resistant Bacteria composed of non-Federal experts.

The DNARP should, working with the relevant agencies, rapidly develop a National Action Plan for Antibiotic Resistance. Building on the recommendations in this report, the National Action Plan should lay out measurable goals and timelines for public health activities, improved surveillance systems, increased discovery and development of new antibiotics, and better stewardship of existing antibiotics in health care and agriculture with particular attention to microbes classified by CDC as urgent or serious threats.

Recommendation 2. Effective Surveillance & Response for Antibiotic Resistance

(1) Strengthen State and local public health infrastructure for surveillance and response.

CDC should expand its funding to State and local public health departments to enhance programs for detection of antibiotic resistance, outbreak response, and aggressive prevention activities across health care and community settings, including enhanced stewardship programs. HHS should allocate to CDC \$90 million of new funding to support 60 grants to States, the District of Columbia, Puerto Rico and major cities for public health efforts for detection of antibiotic resistance, outbreak response, and aggressive prevention activities that address stewardship of existing antibiotics and address community diseases such as multi-drug resistant gonorrhea and TB in high-risk areas.

(2) Establish a national capability for pathogen surveillance based on genome analysis.

The national capability should include (1) a national laboratory network for pathogen surveillance, (2) a reference collection of genome sequences from diverse antibiotic-resistant isolates, (3) development of new computational methods and tools, (4) a publicly accessible database

together with analytical tools, (5) undertaking surveillance efforts in diverse settings, and (6) the development of surveillance and testing standards.

Building this capability and maintaining standards of operation will require cooperation and coordination among CDC, FDA, USDA, the National Institutes of Health (NIH), DoD, VA, and the National Institute of Standards and Technology (NIST), with CDC playing a lead role in establishing the network. We estimate that creating and maintaining a national surveillance capability based on genome analysis will ultimately cost \$190 million per year.

Recommendation 3. Fundamental Research

(1) Expand fundamental research relevant to developing new antibiotics and alternatives for treating bacterial infections. The Administration should request dedicated funds for NIH and FDA to support fundamental research aimed at understanding and overcoming antibiotic resistance, and for Defense Advanced Research Projects Agency (DARPA) and Defense Threat Reduction Agency (DTRA) to support non-traditional approaches to overcoming antibiotic resistance. An appropriate funding level would be \$150 million per year over 7 years, with rigorous evaluation of its effectiveness at the end of this period. Support should consist of new appropriations, rather than repurposing of existing funds.

(2) Develop alternatives to antibiotics in agriculture. USDA should develop, in collaboration with NIH and the agriculture industry, a comprehensive research and development strategy to promote the fundamental understanding of antibiotic resistance and the creation of alternatives to or improved uses of antibiotics in food animals. One mechanism that should be employed is a USDA multidisciplinary Innovation Institute; the Institute will require \$25 million in annual funding, as was requested in the President's FY15 Budget.

These investments should be considered a distinct research portfolio under the National Action Plan, whose composition is regularly reported to DNARP and whose impact against measurable goals can be directly evaluated.

Recommendation 4. Clinical Trials with New Antibiotics

(1) Establish a robust national infrastructure to support clinical trials with new antibiotics. NIH and FDA should convene industry and other public and private stakeholders to define the requirements for an appropriate clinical trials infrastructure, and NIH and FDA should propose a plan to create such an infrastructure. The estimated annual cost is \$25 million to establish infrastructure and common protocols, with additional funds needed from partnerships for late stage clinical trials.

(2) Develop new regulatory pathways to evaluate urgently needed antibiotics. FDA should use existing mechanisms to facilitate approval of drugs based on demonstration of safety and efficacy in specific patients infected with antibiotic-resistant bacteria, while discouraging use in other patient populations. In parallel, the Administration should support the passage of legisla-

tion that explicitly authorizes the FDA to establish a full Special Medical Use pathway for antibiotics.

Recommendation 5. The Federal Government should significantly increase economic incentives for developing urgently needed antibiotics

The DNARP should evaluate various options, discussed in the report below, for attracting greater private investment in developing new antibiotics, and the White House should then work with the Congress to develop appropriate legislation to authorize and fund incentives. The most feasible path may comprise (1) direct Federal funding of advanced research and development for earlier stage commercial programs or (2) an Antibiotic Incentive Fund to provide advanced market commitments and milestone payments to reward developers with later stage projects. We estimate that effective incentives will require investments of \$800 million by the Federal Government, in partnerships with industry, to yield approximately one new FDA approved antibiotic per year.

Recommendation 6. Improving Stewardship of Existing Antibiotics in Health Care

(1) Centers for Medicare and Medicaid Services (CMS) should use reimbursement incentives to drive antibiotic stewardship.

(1) Stewardship programs in hospitals and long-term care facilities. By the end of 2017, CMS should have Federal regulations (Conditions of Participation) in place that will require U.S. hospitals, critical access hospitals, and long-term care and nursing home facilities to develop and implement robust antibiotic stewardship programs that adhere to best practices. Similar requirements should be phased in rapidly for other settings including long-term acute care hospitals, other post-acute facilities, ambulatory surgery centers, and dialysis centers.

(2) Antibiotic use in outpatient settings. CMS should expand the Physician Quality Reporting System (PQRS) to include quality measures that discourage inappropriate antibiotic use for non-bacterial infections, such as respiratory tract infections. Such measures should be developed in conjunction with subject matter experts from CDC and other relevant stakeholders.

(3) Gathering data on antibiotic use and resistance. CMS should include in the Inpatient Quality Reporting program and reporting on Hospital Compare quality measures based on data reported by health care facilities to the National Health care Safety Network (NHSN) Antimicrobial Use and Resistance (AUR) module. Such quality measures should be ready for submission to the consensus body entity for endorsement by 2017, and implementation consideration through the Measure Application Partnership by 2018. HHS should ensure that annually CDC has the budget needed to purchase commercial data on drug purchases and other outpatient prescribing practices.

(2) The Federal Government should use funding requirements to drive antibiotic stewardship.

Federal agencies should require implementation of antibiotic stewardship programs as a condition for receiving Federal grants for health care delivery, including in community health care centers.

(3) The Federal Government should lead by example in antibiotic stewardship in its own health care facilities. Health care delivery facilities operated by the Federal Government should (1) work with CDC to develop and implement antibiotic stewardship programs, and (2) report to the Antimicrobial Use and Resistance module of the NHSN.

(4) Prizes for the development of breakthrough diagnostics. HHS should create Global Challenge Inducement Prizes for the development of rapid, inexpensive, and clinically relevant diagnostics that can substantially improve therapy in important clinical settings. Prizes might be in the range of \$25 million each, supported by Federal funding with additional funding potentially from foundations or other nations.

Recommendation 7. Limit the Use of Antibiotics in Animal Agriculture

PCAST strongly supports FDA's new Guidances 209 and 213, designed to promote the judicious use of antibiotics in agriculture.

(1) FDA should proceed vigorously with the implementation of these guidances, including completing its rulemaking to update the language of the Veterinary Feed Directive.

(2) USDA, through its Cooperative Extension Service, should establish and lead a national education program to help meat producers comply with the FDA guidances and licensed veterinarians understand their new roles in overseeing antibiotic use.

(3) FDA should assess progress by monitoring changes in total sales of antibiotics in animal agriculture and, where possible, in usage of antibiotics; and by developing and undertaking studies to assess whether decreases are observed in antibiotic resistance among farm animals.

If the FDA guidances are not effective in mitigating the risk of antibiotic resistance associated with antibiotic use in animal agriculture, FDA should take additional measures.

Recommendation 8. Ensure Effective International Coordination

The Federal Government should vigorously support development of the World Health Organization (WHO) Global Action Plan and continue to elevate the issue of antibiotic resistance to the level of a global priority by encouraging or requiring, as appropriate, coordination among countries for surveillance, reporting, research, antibiotic stewardship, and development of new and next-generation drug and diagnostics development.



Introduction

For an American in the 21st century, it is hard to imagine the world before antibiotics.¹ At the beginning of the 20th century, as many as nine women out of every 1,000 who gave birth died, 40 percent from sepsis.² In some cities as many as 30 percent of children died before their first birthday.³ One of every nine people who developed a serious skin infection died, even from something as simple as a scrape or an insect bite.⁴ Pneumonia killed 30 percent of those who contracted it;⁵ meningitis killed 70 percent.⁶ Ear infections caused deafness; sore throats were not infrequently followed by rheumatic fever and heart failure. Surgical procedures were associated with high morbidity and mortality due to infection.

This picture changed dramatically with three major developments: improvements in public health, vaccines, and antibiotics. Over the course of the 20th century, deaths from infectious diseases declined markedly and contributed to a 29.2-year increase in life expectancy.⁷ Antibiotics, in particular, have saved millions of lives. First developed in the 1930s, they became widely available starting in the mid-1940s. They have also facilitated a wide range of medical advances – such as burn management, open-heart surgery, and solid organ and bone marrow transplantation – in which the ability to prevent and control infection is essential.

But, the United States and the world are now at dire risk of losing this progress. Bacteria and other microbes evolve in response to their environment and inevitably develop mechanisms to resist being killed by antibiotics. The emergence of drug resistance occurs through natural selection – that is, microbes carrying randomly arising mutations and newly acquired genes that improve their ability to reproduce in the presence of antibiotics will outgrow microbes sensitive

¹ In this report, the term ‘antibiotics’ refers to antibacterials, although similar considerations apply to antifungals. The report does not focus on antivirals or antiparasitics.

² Centers for Disease Control and Prevention. “Achievements in Public Health, 1900-1999: Healthier Mothers and Babies,” *Morbidity and Mortality Weekly Report*, 48(38): 849-858, 1999. www.cdc.gov/mmwr/preview/mmwrhtml/mm4838a2.htm#fig2.

³ Ibid.

⁴ Spellberg, B, et al. “Antimicrobial Agents for Complicated Skin and Skin-Structure Infections: Justification of Non-inferiority Margins in the Absence of Placebo-Controlled Trials,” *Clinical Infectious Diseases Journal*, 2009, 49 (3): 383-391. cid.oxfordjournals.org/content/49/3/383.full.

⁵ Ratner, AJ and Weiser, JN. “Pneumonia before antibiotics: Therapeutic evolution and evaluation in twentieth-century America,” *Journal of Clinical Investigation*, 116(9): 2311, 2006.

⁶ Raghunathan, PL, Bernhardt, SA, Rosenstein, NE. “Opportunities for Control of Meningococcal Disease in the United States,” *Annual Review of Medicine*, 55: 333-353, 2003. www.cdc.gov/vaccines/pubs/surv-manual/chpt08-mening.html#f7.

⁷ Centers for Disease Control and Prevention. “Achievements in Public Health, 1900-1999: Healthier Mothers and Babies,” *Morbidity and Mortality Weekly Report*, 48(38): 849-858, 1999. www.cdc.gov/mmwr/preview/mmwrhtml/mm4838a2.htm#fig2.

to antibiotics. Penicillin-resistant strains of *Staphylococcus aureus* were first reported in the late 1940s, shortly after penicillin became widely available for clinical use, and physicians began to note the appearance of drug-resistant organisms.⁸ Alexander Fleming, recipient of the Nobel Prize for his discovery of the antibiotic penicillin, highlighted the potential problem in his speech at the Nobel Banquet in Stockholm in 1945, warning of “the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”⁹ For many decades, however, the problem was manageable as the growth of resistance was slow and the pharmaceutical industry continued to create new antibiotics.

Over the past decade, however, this brewing problem has become a crisis. The evolution of antibiotic resistance is now occurring at an alarming rate and is outpacing the development of new countermeasures capable of thwarting infections in humans.¹⁰ This situation threatens patient care, economic growth, public health, agriculture, economic security, and national security. Various groups, including the Infectious Disease Society of America (IDSA),¹¹ have called attention to the resistance problem and attempted to advance solutions.

Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) each recently identified antibiotic resistance as one of the greatest threats to human health worldwide.^{12,13} CDC estimates that each year more than two million people in the United States are sickened with infections by more than 17 types of antibiotic-resistant microbes (Appendix C). More than 23,000 Americans die annually as a direct result of these infections, with many more dying from related conditions, such as *Clostridium difficile* (*C. difficile*)-associated disease. CDC emphasizes that these may well be conservative estimates based on the limited data available.

According to CDC, the annual domestic impact of antibiotic-resistant infections to the U.S. economy has been estimated to be \$20-35 billion in excess direct health care costs, with additional costs to society for lost productivity as high as \$35 billion per year and 8 million addition-

⁸ (1) Rammelkamp, CH and Maxon, T. “Resistance of *Staphylococcus aureus* to the Action of Penicillin,” *Proceedings of the Society for Experimental Biology and Medicine*, 51:386-389, 1945; (2) Barber, M. “Staphylococcal Infections Due to Penicillin-resistant Strains,” *British Medical Journal*. 1947; (3) Bondi, JA and Dietz, CC. “Penicillin Resistant Staphylococci,” *Proceedings of the Society for Experimental Biology and Medicine*, 1945; (4) Lowy, FD. “Antimicrobial Resistance: The Example of *Staphylococcus aureus*,” *Journal of Clinical Investigation*, 111(9):1265-1273; (5) “Abuse of Antibiotics,” *The Lancet*, 265(6873):1059-1060, 1955.

⁹ Fleming, A. Nobel lecture on penicillin. Stockholm, Sweden, December 11, 1945.

http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf.

¹⁰ Centers for Disease Control and Prevention. “Antibiotic Resistance Threats in the United States,” 2013. www.cdc.gov/drugresistance/threat-report-2013.

¹¹ Spellberg, B, Blaser, M, et al. “Combating Antimicrobial Resistance: Policy Recommendations to Save Lives,” *Clinical Infectious Disease Journal*, 5: S397-428, 2011.

¹² Centers for Disease Control and Prevention. “Antibiotic Resistance Threats in the United States,” 2013. www.cdc.gov/drugresistance/threat-report-2013.

¹³ World Health Organization. “2014 Global Report on Antimicrobial Resistance,” 2014. http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1.

al days in hospitals.¹⁴ The safety of many modern medical procedures relies on effective antibiotics – cancer chemotherapy, complex surgery, dialysis for renal disease, and organ transplantation become significantly more dangerous as bacterial resistance rises.

Moreover, antibiotic resistance affects many millions of people globally. In developing countries, the problem is compounded by a lack of basic health care and public health infrastructure; low rates of vaccination; inadequate access to clean water; a shortage of trained health care providers; indiscriminate access to over-the-counter antibiotics in pharmacies; sub-standard quality of available antibiotics; counterfeit and mislabeled antibiotics; and limited availability of drugs in certain cases (particularly of newer drugs, if a resistant infection is suspected). Antibiotic-resistant bacteria do not respect borders. Resistant strains that arise in one part of the world can – and do – spread rapidly to other parts of the world, due to increased international travel and globalized trade.

Levels of antibiotic resistance have now reached the point where some bacteria have become resistant to most or all available antibiotics (sometimes referred to as ‘super bugs’):

- In March 2013, CDC issued a *Vital Signs* report alerting the medical community and general public to one group of ‘nightmare bacteria’, carbapenem-resistant Enterobacteriaceae (CRE), which are now resistant to nearly all known antibiotics and kill up to 50 percent of people infected. CRE, which is often associated with urinary tract infections, was first detected in a single patient in 1996, and has now been identified in 47 states¹⁵ and every WHO region.
- *C. difficile*-associated disease accounts for approximately 250,000 infections requiring hospitalization each year, and results in 14,000 deaths in the United States. This debilitating condition, caused by a bacterial infection, is directly related to antibiotic use and resistance.
- Extensively drug-resistant tuberculosis (XDR-TB) has now been reported in 92 countries and comprises an increasing proportion of drug-resistant TB cases.¹⁶ XDR-TB is resistant to virtually all known antibiotics. For example, a cluster of XDR-TB patients occurred in 2006 in Tugela Ferry, South Africa. Of 53 patients (all of whom were also infected with HIV), 52 died within three weeks after diagnosis (98 percent mortality).¹⁷

¹⁴ Roberts, RR, Hota, B, Ahmad, I, et al. “Hospital and Societal Costs of Antimicrobial-resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship,” *Oxford Journal of Clinical Infectious Disease*, 49(8): 1175-1184, 2009. www.tufts.edu/med/apua/consumers/personal_home_5_1451036133.pdf.

¹⁵ Thomas R. Frieden. “Why Global Health Security Is Imperative,” *The Atlantic*, 2014.

<http://www.theatlantic.com/health/archive/2014/02/why-global-health-security-is-imperative/283765/>

¹⁶ XDR TB is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). See CDC Factsheet: www.cdc.gov/tb/publications/factsheets/drtb/xdrtb.htm.

¹⁷ O’Donnell, MR, Padayatchi, N, et al. “Treatment Outcomes for Extensively Drug-Resistant Tuberculosis and HIV Co-infection,” *Emerging Infectious Diseases Journal*, 19(3), 2013. www.cdc.gov/eid/article/19/3/12-0998_article.htm.

- The microbe responsible for gonorrhea is becoming resistant to third-generation cephalosporins, the last available single-agent therapy that is easy to give to outpatients. Treatment failure has been confirmed in at least ten countries, including Austria, Australia, Canada, France, Japan, Norway, Slovenia, South Africa, Sweden, and the United Kingdom. If full resistance emerges, the regimens required for treatment will become more complex, more toxic, and extremely difficult to give in the outpatient setting, greatly jeopardizing control of these infections.
- Concerns are growing about the spread of resistance among organisms responsible for more common infections, such as fluoroquinolone-resistant *E. coli* (usually associated with urinary tract infections and infections of the upper urinary tract known as pyelonephritis).¹⁸

In some cases, aggressive public health and infection-control measures have been able to decrease the prevalence of antibiotic resistance.¹⁹ But, these measures alone are not enough to solve the problem.

A variety of issues are relevant to the rise of antibiotic resistance:

- **Human Health Care.** Antibiotics are among the most commonly prescribed drugs used in human medicine. The CDC estimates, however, that up to 50 percent of all the antibiotics prescribed for patients in the United States are not needed or are not optimally prescribed.²⁰ Reasons for antibiotic overuse in health care include concern about not treating an infection even when infection is unlikely; lack of rapid, accurate, and well-validated point-of-care diagnostic tests; pressure from the patient (or the patient's family) due to insufficient understanding of antibiotic use; physician time constraints that limit the opportunity to educate patients; and marketing to physicians by pharmaceuti-

¹⁸ Hwang, TJ and Hooper, DC. "Association between Fluoroquinolone Resistance and Resistance to Other Antimicrobial Agents among *Escherichia coli* Urinary Isolates in the Outpatient Setting: A National Cross-sectional Study," *Journal of Antimicrobial Chemotherapy*, 69(6): 1720-1722, 2014.

¹⁹ Examples include: (1) aggressive responses to CRE by Israel (Schwaber, MJ and Carmeli, Y. "An Ongoing National Intervention to Contain the Spread of Carbapenem-resistant Enterobacteriaceae," *Clinical Infectious Diseases*, 58 (5): 697-703, 2014), (2; 3) which prompted actions in the United States (Chitnis, AS, et al. "Outbreak of Carbapenem-Resistant Enterobacteriaceae at a Long-Term Acute Care Hospital: Sustained Reductions in Transmission through Active Surveillance and Targeted Interventions," *Infection Control and Hospital Epidemiology*, 33 (10): 984-992, 2012; Centers for Disease Control and Prevention. "Carbapenem-Resistant Enterobacteriaceae Containing New Delhi Metallo-Beta-Lactamase in Two Patients — Rhode Island, March 2012," *Morbidity and Mortality Weekly Report*, 61(24):446-448, 2012. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6124a3.htm>.) and (4) against MRSA in the United Kingdom (Johnson, AP, et al. "Mandatory Surveillance of Methicillin-resistant *Staphylococcus aureus* (MRSA) Bacteraemia in England: The First 10 Years," *The Journal of Antimicrobial Chemotherapy*, 67(4): 802-809, 2012).

²⁰ Hecker, MT, Aron, DC, et al. "Unnecessary Use of Antimicrobials in Hospitalized Patients: Current Patterns of Misuse with an Emphasis on the Antianaerobic Spectrum of Activity," *Archives of Internal Medicine*, 163: 972-978, 2003.

cal companies.²¹ The misuse and overuse of antibiotics in human medicine, both in the United States and internationally, is a major contributor to rising antibiotic resistance.

- **Animal Agriculture.** Medically important antibiotics are also extensively used in animal agriculture not only to treat sick animals, but also to promote animal growth and to prevent infections.²² All of these uses can promote the development of antibiotic resistance among bacteria in animals, and these resistant strains can spread to humans. While the extent to which antibiotic resistance in animal agriculture contributes to human infections is not known, the risks to human health posed by the agricultural use of antibiotics is, appropriately, a matter of very serious concern.
- **Drug Development.** The world lacks a robust pipeline of new antibiotics to replace those being steadily lost to antibiotic resistance. The number of new systemic antibacterial agents approved by the Food and Drug Administration (FDA) has decreased steadily over the past three decades: 16 (1983-1987), 14 (1988-1992), 10 (1993-1997), 7 (1998-2002), 5 (2003 to 2007), 2 (2008-2012), and 1 since 2013.²³ The lack of new drugs is particularly concerning for life-threatening Gram-negative bacteria.²⁴ The drug development pipeline is failing for a variety of reasons – including scientific challenges in discovering and developing new drugs; practical challenges in conducting the clinical trials needed for new-drug approval; and low economic returns that have made the development of new antibiotics an unattractive investment. As a result, large pharmaceutical companies have decreased or eliminated their investments in antibiotic drug development. In fact, fewer than 5 of the largest 50 pharmaceutical companies currently have active antibiotic-development programs.²⁵
- **Surveillance and Response.** Situational awareness is crucial for addressing national and international threats. Yet, the United States currently lacks comprehensive monitoring for antibiotic resistance emerging domestically and being imported from abroad. Our surveillance systems are woefully underfunded and as a result our situational awareness remains rudimentary. Powerful tools that emerged from the Human Genome Project have the ability to reveal how antibiotic resistance arises and spreads across health care facilities, agriculture, the environment, and international borders, but they are not being routinely used. And adequate public and animal health infrastructure for monitoring an-

²¹ Barden, LS, et al. "Current Attitudes Regarding use of Antimicrobial Agents: Results from Physician's and Parents' Focus Group Discussions," *Clinical Pediatrics*. 37(11): 665-671, 1998.

²² Animal agriculture also uses classes of antibiotics, such as ionophores, that are not used in human medicine.

²³ (1) Boucher, HW and Talbot, GH. "10 x'20 Progress—Development of New Drugs Active Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America," *Oxford Journal of Clinical and Infectious Diseases*, 2013; (2) Spellberg B, Powers JH, et al. "Trends in Antimicrobial Drug Development: Implications for the Future," *Journal of Clinical and Infectious Disease*, 38: 1279–1286, 2004; (3) May, M. "Outlook: Antibiotics," *Nature*, 509: S1-S17, 2014.

²⁴ Bacteria are classified as 'Gram-negative' because they do not stain with a diagnostic chemical, crystal violet, due to the nature of their cell wall.

²⁵ More generally, PCAST's September 2012 Report on *Propelling Innovation in Drug Discovery, Development, and Evaluation* addressed stresses in the innovation ecosystem for public health.

tibiotic use and resistance and responding both to outbreaks and ongoing problems with resistant infections is lacking in many states and localities.

In November 2013, President Obama tasked his President's Council of Advisors on Science and Technology (PCAST) with making practical and actionable recommendations concerning how the Federal Government can best combat the rise of antibiotic resistance that is threatening the health of Americans and people around the world. To respond to this request, we rapidly assembled a taskforce of 15 non-Federal experts in the field of antibiotic resistance and also consulted with experts across Federal agencies. Informed by extensive discussions with these experts, PCAST developed this report.

In the fight against microbes, no permanent victory is possible: as new treatments are developed, organisms will evolve new ways to become resistant. Yet, ongoing success is possible by making three fundamental shifts:

- (1) **improving our surveillance of the rise of antibiotic-resistant bacteria** to enable effective response, stop outbreaks, and limit the spread of antibiotic-resistant organisms, and acting on surveillance data to implement appropriate infection control;
- (2) **increasing the longevity of current antibiotics**, by improving the appropriate use of existing antibiotics, preventing the spread of antibiotic-resistant bacteria and scaling up proven interventions to decrease the rate at which microbes develop resistance to current antibiotics;
- (3) **increasing the rate at which new antibiotics, as well as other interventions, are discovered and developed.**

PCAST recommends in this report a number of high priority steps that the Federal Government should take to achieve these goals.



I. Federal Investment and Leadership: Making Antibiotic Resistance a National Priority

Success in combating antibiotic resistance will require elevating the issue to a national priority. The crisis in antibiotic resistance comes as no surprise: it has been brewing for decades, despite urgent calls from medical experts dating back as far as the 1940s and 1950s.²⁶ Yet, the issue has only just begun to seize public attention, due to increasing high rates of resistant pathogens in health care facilities.

1.1 Federal Investments

In PCAST's view antibiotic resistance has received inadequate national attention over the past quarter century. Federal spending has been limited – approximately \$450 million in direct funding in FY14, corresponding to just over \$1.40 per American. Funds are allocated across the Department of Health and Human Services (approximately \$300 million), the Department of Veterans Affairs (approximately \$60 million), Department of Defense (approximately \$50 million) and Department of Agriculture (less than \$20 million). The uses include basic and applied research (about 75% of total funding), stewardship in human health care (approximately 15%), surveillance in human health care (only approximately 5%), and agricultural programs (only approximately 5%).

The approximately \$450 million devoted to combating antibiotic resistance is dwarfed by the staggering annual impact on the United States, as noted in the previous section:

- two million people infected per year;
- 23,000 deaths per year as a direct result of antibiotic-resistant pathogens, with many more from conditions complicated by drug-resistant infections;
- \$55-70 billion per year in economic impact, including \$20-35 billion in excess direct health care costs and additional costs in lost productivity.

Moreover, the impact is growing with each passing year.

Federal actions that reduce the impact of antibiotic resistance by, for example, 30 percent

²⁶ (1) Spink, WW and Ferris, V. "Penicillin-resistant Staphylococci: Mechanisms Involved in the Development of Resistance," *Journal of Clinical Investigation*. 26: 379–393, 1947; (2) Finland, M, and Haight, TH. "Antibiotic resistance of Pathogenic Staphylococci," *American Medical Association Archives of Internal Medicine*, 91: 143-158, 1953; (3) Dowling, HF, Lepper, HF and Jackson, GG. "Observations on the Epidemiological Spread of Antibiotic-Resistant Staphylococci with Measurements of the Changes in Sensitivity to Penicillin and Aureomycin," *American Journal of Public Health and the Nation's Health*, 43(7): 860-868, 1953; (4) Dowling, HF, Lepper, MH and Jackson, GG. "Clinical Significance of Antibiotic Resistant Bacteria," *Journal of the American Medical Association*, 157: 327-331, 1955.

would save many thousands of lives and approximately \$20 billion in costs per year, including decreasing Medicare expenditures. Moreover, these investments would have an even greater impact if the investments created infrastructure that truly shifted the long-term balance in the struggle with microbes, including by providing an ‘early warning system’ for resistant microbes.

In this report, PCAST recommends an integrated set of Federal actions to address the antibiotic resistance crisis. These actions will require a substantial increase to the current Federal investment:

- Undertaking a variety of core activities (to strengthen public health infrastructure, create a robust microbial surveillance infrastructure, support research, increase the efficiency of clinical trials and support transformative diagnostics) will require approximately an additional \$450 million per year – that is, roughly doubling the Federal investment from the current \$450 million per year to \$900 million per year.

- The Federal Government will also need to create economic incentives to elicit greater private investment in developing new antibiotics. We offer alternative approaches (including direct Federal support for research and development for early stage products, higher reimbursement rates, incentive payments for later stage products, and tradable vouchers to extend patent lives on other drugs). While the alternatives should be carefully reviewed by the coordination and leadership structure recommended below, we believe that the most feasible approach may be support by the Biomedical Advanced Research and Development Authority (BARDA).²⁷ If so, we recommend funding of \$800 million per year to BARDA to support partnerships with industry. Together with increased support for fundamental research and increased efficiency for clinical trials recommended in this report, this funding level might translate into one new antibiotic per year.

The specific costs underlying these investment and incentive totals are integrated into the recommendations throughout this report. While mindful of current pressures on the Federal budget, PCAST believes that such investments are clearly justified given the current magnitude of the public health and economic impacts, the likelihood that resistance will continue to grow into the future, and the potential savings to the Nation if the Federal Government initiates aggressive and coordinated, multi-sectoral actions immediately.

1.2 Federal coordination and leadership

Increased Federal investments will only be justified if the funds are well spent and well managed. Fifteen years ago, the Federal Government created an Interagency Task Force on Antimicrobial Resistance (ITFAR).²⁸ Without a full-time Director, ITFAR is co-chaired by CDC, FDA, and

²⁷ Created in 2006, the Biomedical Advanced Research and Development Authority (BARDA), within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services, provides an integrated, systematic approach to the development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies, including pandemic influenza and other emerging infectious diseases.

²⁸ The Interagency Task Force on Antimicrobial Resistance was established informally in 1999 following congressional interest by Senators Frist and Kennedy. In 2000, Congress passed HR 2498 (Public Health Improvement Act)

the National Institutes of Health (NIH), and includes representatives of twelve Federal agencies. While the ITFAR has led to increased interagency cooperation on technical issues, it has not succeeded in generating the kind of overarching Federal response and accountability needed to effectively address antibiotic resistance. In PCAST's judgment, ITFAR is not an adequate solution for ensuring a robust Federal strategy and implementation to combat antibiotic resistance and should be replaced by a more effective structure.

PCAST believes that stronger leadership is needed to develop effective plans and milestones, articulate clear roles and responsibilities for lead agencies, ensure accountability in meeting key milestones, and sustain national commitment to a multi-year challenge.

A useful analogy is this Administration's development of national policy for HIV/AIDS. At the beginning of the Administration, the President instructed the White House Office of National AIDS Policy (ONAP) to develop a national HIV/AIDS policy and refocus the Nation's approach to the HIV epidemic. On the day that the National HIV/AIDS Strategy was released in 2010, the President issued a Presidential Memorandum to ensure coordination, collaboration, and accountability across the Federal Government in support of the strategy. The Memorandum tasked the ONAP Director with establishing national priorities and monitoring implementation, and assigned departments and agencies with developing operation plans and designated clear roles and responsibilities. The President also included, within his proposed budget, a specific line item within the broader appropriation to the Executive Office of the President. Before these actions, ONAP lacked such a clear role and adequate resources to achieve its mission. These steps appear to have been effective, and they have won support from the HIV/AIDS community.

PCAST recommends that the President:

- task the National Security Council, in coordination with the Office of Science and Technology Policy and the Office of Management and Budget (OMB), with oversight and coordination of Federal efforts to combat antibiotic resistance.
- appoint a member of the National Security Council Staff as White House Director for National Antibiotic Resistance Policy (DNARP), reporting directly to both the Assistant to the President for Homeland Security and Counterterrorism and to the Director of OMB and supported by adequate professional staff, devoted fully to ensuring integration and accountability and reporting annually on the state of progress.
- establish an interagency Task Force on Combating Antibiotic-Resistant Bacteria (TF-CARB) co-chaired by the Secretaries of Agriculture, Defense, and Health and Human Services or their designated deputies, and including all relevant agencies.

which instructed the Secretary of Health and Human Services to establish "an Antimicrobial Resistance Task Force to provide advice and recommendations to the Secretary on Federal programs relating to antimicrobial resistance." The law also required "(1) research and development of new antimicrobial drugs and diagnostics; (2) educational programs for medical and health personnel in the use of antibiotics; and (3) grants to establish demonstration programs promoting the judicious use of antimicrobial drugs and the control of the spread of antimicrobial-resistant pathogens." The ITFAR released the Public Health Action Plan to Combat Antimicrobial Resistance in 2001, which was updated in 2012.

- under the auspices of TF-CARB, establish a Joint Scientific Working Group on Human Antibiotic Resistance (JSWG-HAR), consisting of staff from CDC, FDA, and NIH, to coordinate and undertake projects focused on human health among the three agencies.
- establish a President’s Advisory Council on Combating Antibiotic-Resistant Bacteria, composed of non-Federal experts, as a committee under the Federal Advisory Committee Act.

The DNARP will play a particularly important role, as the locus of integration and accountability. The DNARP should have responsibility for rapidly developing an integrated National Action Plan to combat antibiotic resistance based on input from the Federal agencies. The National Action Plan should include clear metrics and milestones, including specific goals and timelines for addressing each of the microbes classified by CDC as urgent or serious threats. The DNARP should monitor progress on implementation of the National Action Plan and issue an annual progress report to the President. Working with TF-CARB, the DNARP should convene Federal agencies and focus resources to address challenges preventing full implementation. The DNARP should also engage with the state and local government, academic, health care, biotechnology and pharmaceutical, and agricultural sectors, as well as with the Nation’s international partners to address the challenge of antibiotic resistance.



II. Monitoring Antibiotic Resistance: Systematic Surveillance and Response Capacity

Combating antibiotic resistance requires systematic surveillance and rapid outbreak response. Surveillance – that is, the ability to systematically collect and analyze samples, isolates, and associated data to ascertain the presence, prevalence, and specific characteristics of antibiotic-resistant bacteria – is essential for detecting resistant pathogens, tracing their spread, and inferring their origin.

Real-time tracking of antibiotic-resistant bacteria in health care settings enables the early identification of outbreaks and rapid response to prevent the spread of antibiotic-resistant bacteria from patient to patient, between health care facilities, and from health care facilities into the community.

Crucial surveillance questions include the following:

- Is a particular individual infected (or colonized) with a given resistant pathogen?
- What is the prevalence of antibiotic resistance in a given pathogen in a particular health care facility, city, or state?
- Do multiple cases in a health care facility reflect transmission within the facility, or independent introductions of the pathogen? In the first case, how can infection control practices be improved to prevent the outbreak from growing? In the second case, can these strains be traced to specific other locations? In either case, have other patients been exposed, and can disease be averted?
- If a resistant pathogen appears in a patient who had been previously treated for infection caused by this organism, does this represent reinfection by a new resistant strain or inadequate treatment for the earlier infection?
- Did a resistant pathogen circulating in a U.S. city arise in a health care facility, elsewhere in the community, on a farm, or in a foreign country? What was the ‘flow’ of resistance among these different reservoirs?

Distressingly, the answers to these straightforward questions are often unknown. The first two questions involve detecting the presence of antibiotic resistance; this can be accomplished via traditional clinical laboratory testing and data collection. The frequent lack of knowledge can be traced, in many cases, to the absence of state requirements to collect antibiotic resistance data

and to inadequate public health infrastructure for surveillance. In contrast, the latter three questions involve tracing the precise origins of bacteria and enforcing best practices. With traditional methods of characterizing antibiotic-resistant bacteria, it was difficult to answer these questions. In the past few years, however, advances in rapid and inexpensive DNA-sequencing technology have made it possible to extract answers from bacterial genomes.²⁹

Epidemiological and genomic information gathered from systematic surveillance needs to be integrated and utilized rapidly and effectively to respond to antibiotic-resistant threats. Surveillance can reveal the most critical resistance problems in a community and help guide appropriate responses. It can also give early indications of outbreaks of new or growing resistant pathogens, where rapid response is essential to prevent the spread of resistant pathogens and save lives. Effective, evidence-based strategies to control the spread of resistant bacteria have been proven to work, but they need to be implemented consistently and broadly within communities and regions to prevent resist organisms from spreading within hospitals, between health care facilities, and from health care settings into the community.

Beyond the U.S. health care system, a national network for microbial resistance would have other important uses:

- It would support collaborative efforts with international partners to substantially improve situational awareness of antibiotic resistance beyond the Nation's borders.
- It would enable the collection of critical information about antibiotic-resistant organisms in animal agriculture, in food, and in the environment – consistent with the CDC's One Health concept that recognizes that the health of humans is closely connected to the health of animals and the environment.
- Finally, it would enhance national biodefense security – by providing an early detection system for new microbial threats.

2.1 Strengthen State and local public health infrastructure for surveillance and response

Public health surveillance is critical for rapidly identifying patients infected or colonized with an antibiotic-resistant organism who might spread the pathogen to others. Notably, current public health resources were not adequate to detect and contain the recent emergence and transmission of two deadly bacteria, community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) and carbapenem-resistant Enterobacteriaceae (CRE), as shown by the rapid spread of these organisms in communities and health care settings throughout the United States.³⁰

Most State and local public health departments currently lack adequate capacity to: (1) collect

²⁹ Earlier genomic characterization, using techniques such as pulsed field gel electrophoresis, have played a useful role in epidemiologic investigation, although these methods are now outdated and provide limited information.

³⁰ (1) Bratu, S, et al. "Rapid Spread of Carbapenem-resistant *Klebsiella pneumoniae* in New York City: A New Threat to Our Antibiotic Armamentarium," *Archives of Internal Medicine*, 165: 1430-1435, 2005; (2) Wertheim, et al. "Low Prevalence of Methicillin-resistant *Staphylococcus aureus* (MRSA) at Hospital Admission in the Netherlands: The Value of Search and Destroy and Restrictive Antibiotic Use," *Journal of Hospital Infection*, 56: 321-325, 2004.

relevant epidemiologic and clinical data related to antibiotic-resistant infections across the spectrum of health care delivery; (2) respond to reports of antibiotic-resistant infections of high consequence or concern; and (3) perform basic characterization of resistant pathogens to support case investigation, outbreak response, and prevention activities. These deficiencies can lead to substantial bottlenecks or delays in the event of major outbreaks.³¹

Very limited financial support is dedicated to monitoring and preventing antibiotic resistance in State health departments. What little financial support that exists is provided through CDC's infectious disease cooperative agreements. Current funding includes a total of less than \$10 million for these activities across all 50 States. Even this minimal funding level has resulted in some early successes.³² But, considerably more funding is needed. CDC has undertaken a detailed analysis that indicates that annual funding of approximately \$60 million is needed to bring State and local health departments up to a minimum level of capacity to deal with antibiotic resistance surveillance, prevention, and response activities in health care settings. Additional resources of approximately \$30 million per year are needed in high-risk areas to address some of the unique threats posed by community-transmitted pathogens, such as multi-drug resistant gonorrhea and tuberculosis.

PCAST believes that such investments in public health infrastructure are enormously important and – at an average of approximately \$2 million per State – extremely cost-effective.

2.2 Establish a national capability for pathogen surveillance based on genome analysis

With traditional methods of characterizing antibiotic-resistant bacteria, it was impossible to accurately trace the origin and spread of microbes across patients, facilities, farms, and international borders. The information contained in a bacterium's genome (that is, its complete DNA sequence), however, provides a powerful way to trace the relationship among strains and among samples, based on DNA differences that accumulate as bacteria multiply over many generations. These genetic differences can be used to construct a 'family tree', making it possi-

³¹ The delays in detecting the 2011 outbreak of *E.coli* O104:H4 in Germany demonstrate all these issues. (Altmann, M, et al. "Timeliness of Surveillance during Outbreak of Shiga Toxin-producing *Escherichia coli* Infection, Germany, 2011," *Emerging Infectious Diseases*, 17(10), 2011. http://wwwnc.cdc.gov/eid/article/17/10/11-1027_article.htm.)

³² (1) Oregon has used CDC funding to support their Oregon MDRO project, which is designed to detect, control and prevent infections by multidrug resistant organisms (MDROs) and involves 140 long-term care facilities, 62 acute care hospitals and 48 laboratories. (Pfeiffer, CD, et al. "Establishment of a Statewide Network for Carbapenem-Resistant Enterobacteriaceae Prevention in a Low-Incidence Region," *Infection Control and Hospital Epidemiology*, 35: 356-361, 2014.) (2) Wisconsin has utilized funding to implement an innovative approach to building infrastructure by partnering with the Milwaukee Health Department for prevention strategies across multiple healthcare settings to reduce CRE. (Wisconsin Division of Public Health. "Guidance for Preventing Transmission of Carbapenem-resistant Enterobacteriaceae (CRE) in Acute Care and Long-Term Care Hospitals," 2014. <http://www.dhs.wisconsin.gov/publications/P0/p00532a.pdf>; Wisconsin Division of Public Health. "Guidance for Preventing Transmission of Carbapenem-resistant Enterobacteriaceae (CRE) in Skilled Nursing Facilities," 2014. <http://www.dhs.wisconsin.gov/publications/P0/p00532.pdf>.)

ble to trace the origin of an outbreak of infection caused by resistant bacteria. In a clonal outbreak consisting of a single distinct organism within a health care facility, the bacteria will typically have nearly identical genomes. By contrast, independent introductions of bacteria into a health care facility will typically show many telltale genetic differences. Genome analysis has already been employed in a handful of outbreaks,³³ but its use so far has been rare.

Until recently, routine DNA sequencing of microbial isolates would have been prohibitively expensive. Federal investments in the Human Genome Project and subsequent biomedical projects, however, have propelled dramatic technology advances in DNA sequencing, including by eliciting substantial private investment. The cost of sequencing a human genome is currently about \$2,500 and expected to fall to around \$1,000 by next year (compared to \$3 billion at the start of the Human Genome Project).

These technologies also enable rapid and inexpensive sequencing of bacterial genomes. Generating a high-quality draft genome sequence of a pathogen costs several hundred dollars today, although the majority of the cost is due to sample preparation rather than the actual sequencing. Technologies are already being developed that hold the potential to reduce the total cost to less than \$10 per bacterial genome in the coming years.

PCAST recommends the establishment of a national capability for pathogen surveillance that integrates epidemiological information with genomic sequence and analysis on a routine basis. The goal is not to replace current clinical testing for antibiotic resistance used to make immediate treatment decisions, nor to supplant traditional public health infrastructure; both of these capabilities are essential and must be strengthened. Indeed, this national capability must be integrated into existing public health reporting structures and should serve to strengthen them.

The goal of a high-quality national capability is to obtain sufficient genomic, demographic, clinical and epidemiologic data that will (1) enable situational awareness about the origin and spread of antibiotic resistance that cannot be obtained in any other way, (2) improve outbreak detection and response, (3) provide critical feedback about community, health care, and other facility practices to the facilities themselves as well as to public health entities, and (4) drive the establishment of high technical standards.

Six components are needed:

(1) Establish a national laboratory network for pathogen surveillance. We envision a network of laboratories consisting of (1) regional centers serving diverse facilities and purposes, includ-

³³ (1) Harris, SR, et al. "Whole-genome Sequencing for Analysis of an Outbreak of Methicillin-resistant *Staphylococcus aureus*: A Descriptive Study," *Lancet Infectious Disease*, 13(2): 130-136, 2013. (2) Snitkin, ES, et al. "Tracking a Hospital Outbreak of Carbapenem-resistant *Klebsiella pneumoniae* with Whole-genome Sequencing," *Science Translational Medicine*, 4(148), 2012. (3) Epton, EE, et al. "Carbapenem-resistant *Klebsiella pneumoniae* Producing New Delhi Metallo- β -lactamase at an Acute Care Hospital, Colorado, 2012," *Infection Control and Hospital Epidemiology*, 35(4): 390-397, 2014.

ing health care, agriculture and environmental sampling and (2) clinical laboratories in certain major health care facilities, with the size and balance likely to shift with time and technology.

These laboratories would be able to (1) receive specimens and relevant metadata;³⁴ (2) perform genomic analysis; (3) rapidly return information to providers; (4) rapidly provide information to relevant public health entities, to allow detection of clusters of significant pathogens in the region; (5) archive samples and specimens; and (6) deposit genomic information and metadata in a publicly-accessible national database (see below). Currently, laboratory testing generates limited data on antibiotic resistance for bacterial pathogens.

The network would have multiple purposes. A major purpose would be to support the U.S. health care system, aiding the analysis of clinical specimens and driving improvements in clinical practice and prevention of spread within and between facilities.³⁵ Data and strains collected from the network should be made broadly available to facilitate rapid characterization and study, with appropriate protection of privacy and confidentiality of metadata concerning patients and facilities. In addition, the network would serve as a resource for microbial analysis from food-borne outbreaks, agriculture sites, environmental samples, and international health care sites, in collaboration with international partners.

The DNARP, working with TF-CARB, should convene agencies and other stakeholders to determine the best structure for the network, which should build on recently launched pilot efforts by various agencies.^{36,37} CDC should have responsibility for establishing and maintaining the network of regional laboratories, although the network should include laboratories maintained by other agencies where appropriate. A board chaired by CDC with representatives from FDA, NIH, the Department of Agriculture (USDA), Department of Defense (DoD), and the Department of Veterans Affairs (VA) should oversee the network, to ensure effective decision-making and coordination.

In addition to the network of regional laboratories, NIH should test the approach of establishing a network of clinical laboratories in major health care facilities by providing competitive grants to 10-20 facilities.

We estimate that the annual cost for the two components of the network at \$130 million per year, comprising \$80 million for the regional laboratories and \$50 million for the hospital-based laboratories.

(2) Produce an initial reference collection of genome sequences from diverse antibiotic-resistant isolates, to which specimens analyzed by the network can be compared. CDC has a

³⁴ In the case of a sample from a hospital, the metadata would include such information as basic demographics, date of admission, facility type, date and source of isolate, antibiotic susceptibility profile of isolate, and when possible recent antibiotic therapy.

³⁵ For many hospitals and health care facilities, it will be more effective to use a high-quality national network of regional reference laboratories – provided that it can return answers rapidly. For some large medical centers, however, it may make sense to create their own onsite microbial sequencing capabilities.

³⁶ These efforts include CDC's Emerging Infections Program (EIP) in partnership with health departments in 10 states; NIAID/NIH's Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases; NIAID/NIH's Antibiotic Resistance Leadership Group (described below in Section 4.1); the FDA's NARMS; and FDA's Genome Trackr collaboration, in partnership with CDC and NIH.

³⁷ In addition, CDC and NIH should consult with the National Biodefense Analysis and Countermeasures Center (NBACC) concerning its experience in characterizing biological threats in the context of biodefense.

large repository of well-characterized bacterial pathogens, but few have been sequenced to date. High-quality, fully assembled reference genomes are needed for each of the bacterial species classified by CDC as urgent or serious threats, together with hundreds to thousands of additional DNA sequences to capture genetic diversity of bacterial strains.

CDC and NIH should work as equal partners to generate, within three years, complete genome sequences from a diverse reference collection of antibiotic-resistant pathogens. CDC brings deep expertise concerning the epidemiology of resistant pathogens and an unparalleled sample collection, while NIH has deep expertise in genome sequencing and analysis. Similarly, CDC should work closely with FDA and USDA, which have well characterized strain collections of food-borne pathogens. Academic laboratories can provide a wealth of expertise and innovation for all of these activities.

We estimate the one-time cost for producing the initial reference collection at \$6 million per year for three years.

(3) Support the development of new computational methods and tools, able to carry out genomic analyses of thousands of isolates and specimens. Improved methods and tools are needed for (1) genome assembly and comparison (including identifying horizontal gene transfer and performing microbial source tracking), (2) metagenomic analysis, (3) effective visualization, (4) incorporation of epidemiologic data, and (5) generation of readily interpreted reports to providers. NIH has deep expertise in genomic analysis; it should support extramural projects to develop methods and tools.

We estimate the annual cost of research grants for this development at \$6 million per year.

(4) Create and maintain a publicly accessible database and analysis tools. The database should hold genomic data, phenotypic data and relevant metadata from the reference collection, specimens from the national network, and other sources.

NIH's National Center for Biotechnology Information (NCBI) should take the lead in developing and maintaining databases of genomic information and associated clinical metadata and analysis tools of the types described above for interpreting genomes.

In addition to facilitating the interpretation of clinical isolates, the database will be a rich resource for research on the evolution of pathogens; the genes or mutations that enable them to survive in the presence of powerful antibiotics; antibiotic susceptibility of curated strains; biomarkers for diagnostic development and drug response; and the molecular underpinnings that might make them vulnerable to new drugs. Because bacteria are continually evolving ways to evade antibiotics, CDC and FDA should work with NCBI to update and refine the composition of the genomic database on a regular basis.

We estimate the annual cost to NCBI at \$5 million per year.

(5) Initiate surveillance efforts in diverse settings. The national network for microbial surveillance should serve diverse purposes – including U.S. health care, agriculture, food, environmental sites and non-U.S. health care (in collaborative efforts with international partners). The DNARP and TF-CARB should convene agencies and other stakeholders to develop a comprehensive plan for drawing on the network to address critical national microbial surveillance issues.

The initial focus should be on U.S. health care facilities. CDC should lead these efforts, in coordination with other agencies and with efforts at health care facilities under the DoD and VA.

In addition, pilot projects enabled by the network's capabilities should also be designed and undertaken in other settings. These projects may leverage and expand existing programs, including CDC's Emerging Infections Program (EIP), which can monitor antibiotic-resistant threats outside of health care; the joint FDA, CDC, and USDA National Antimicrobial Resistance Monitoring System (NARMS) which track antibiotic resistance in food-borne bacteria from humans (CDC), retail meats (FDA), and food animals (USDA) and could potentially link human food-borne infections to agriculture and animal reservoirs; and various international collaborations sponsored by NIH.

We estimate the annual cost at \$50 million, including expanding the EIP and NARMS programs.

(6) Develop surveillance and testing standards. The network will help to develop shared standards that should be widely adopted to ensure efficient testing and data analysis. The CDC should continue to work with the Clinical and Laboratory Standards Institute (CLSI) and NIST to develop such standards to improve upon the efficiency, accuracy, and reliability of surveillance and testing protocols for human health care, including antimicrobial susceptibility testing, analysis of clinical isolates and direct detection of resistance by non-culture-based methods. Similarly, USDA should take the lead on establishing standards in veterinary laboratories.

We estimate the annual cost at \$2 million per year.

The establishment of a national infrastructure to generate, analyze and report genomic information from resistant pathogens will drive laboratory and computational progress in microbial-genome sequencing, assembly and analysis. Ultimately, fully automated sample-handling and data analysis methods should allow the analysis of extremely large numbers of samples. Hospitals would be able to routinely monitor the many thousands of resistant isolates identified in their clinical practice.³⁸ Surveillance efforts in other settings would become routine and could provide early warning signs about potential outbreaks, whatever their origin. Tracking patterns across facilities in the community would show patterns of spread to guide preventive interventions.

³⁸ The more than 5,000 hospitals in the United States already culture millions of antibiotic-resistant bacterial isolates from patients each year. For example, over a one year period at Massachusetts General Hospital, a 950-bed tertiary care academic teaching hospital, approximately 18,000 patients were screened for methicillin-resistant *Staphylococcus aureus* (MRSA) colonization of which 5 percent were culture positive, and 23,000 patients were tested for vancomycin-resistant Enterococcus (VRE) colonization of which ~9 percent were culture positive. (MGH Clinical Microbiology Laboratory, email, July 10, 2014). Such samples are currently not stored, but would provide valuable information about the spread of antibiotic resistance.

Recommendation 2. Effective Surveillance and Response for Antibiotic Resistance

(1) Strengthen State and local public health infrastructure for surveillance and response.

CDC should expand its funding to State and local public health departments to enhance programs for detection of antibiotic resistance, outbreak response, and aggressive prevention activities across healthcare and community settings, including enhanced stewardship programs.

HHS should allocate to CDC new funding of approximately \$90 million per year, consisting of (1) approximately \$60 million to support 60 grants to States, the District of Columbia, Puerto Rico, and major cities for these purposes and (2) an additional \$30 million to address community antibiotic resistance threats such as multi-drug resistant gonorrhea and TB in high-risk areas.

(2) Establish a national capability for pathogen surveillance based on genome analysis.

The national capability should include (1) a national laboratory network for pathogen surveillance, (2) a reference collection of genome sequences from diverse antibiotic-resistant isolates, (3) development of new computational methods and tools, (4) a publicly accessible database together with analytical tools, (5) the undertaking of surveillance efforts in diverse settings, and (6) the development of surveillance and testing standards.

As described in the text, the national capability will require cooperation and coordination among multiple agencies. CDC should play a lead role in establishing and maintaining the laboratory network, with FDA, USDA, and NIH playing important roles. NIH should play a key role in creating the reference genome sequences and the database, as well as supporting the development of new methods. CDC, FDA, USDA, NIH, DoD, and VA should all play active roles in undertaking surveillance efforts. NIST should play a central role in standard setting, in partnership with CDC and USDA.

We estimate that creating and maintaining a national surveillance capability based on genome analysis will ultimately cost \$190 million per year.



III. New Antibiotics: Fundamental Research

Fundamental research will be a critical component in overcoming antibiotic resistance. As microbes evolve to evade existing antibiotics, scientists must discover new ways to stay ahead. In human health care, research will be essential for understanding the basis of antibiotic resistance and developing new approaches to antibiotic therapies. In agriculture, research can play an important role in identifying ways to reduce non-therapeutic antibiotic use and reduce the development of antibiotic resistance, including developing new vaccines, probiotics and other alternatives to antibiotics for livestock and poultry.

The European Union has recently expanded its research efforts with respect to antibiotic resistance.³⁹ The United States needs to bring to bear the full energy and creativity of the U.S. research enterprise.

3.1 New approaches to developing antibiotics for human health care

The ability to discover and develop new antibiotics is hampered by major gaps in scientific knowledge and by important limitations in technology. As summarized below, the scientific community is brimming with many scientific and technological ideas with the potential to transform the development of antibiotics.

A particularly important target is Gram-negative bacteria, which account for 9 of the 18 most important antibiotic-resistant or -associated microbial threats in the United States.⁴⁰ Unfortunately, none of the antibiotics that have been approved by the FDA during the past 5 years have activity against this critical group. Moreover, a recent review noted with dismay the lack of *any* drugs in the current global development pipeline with activity against the full spectrum of resistant Gram-negative bacteria.⁴¹

Some examples of new approaches include:

- **Understanding how Gram-negative bacteria block antibiotics from entering or remaining in the cell.** Gram-negative bacteria have been difficult to target for a number of reasons, including that they possess a particularly complex and highly protective outer membrane

³⁹ The European Innovative Medicines Initiative (IMI), a public-private partnership aimed at improving the efficiency of drug discovery and development, has recently launched a project on antibiotics called New Drugs 4 Bad Bugs (ND4BB), with an annual budget of approximately \$70 million. The ND4BB program brings together “industry, academia and biotech organizations to combat antibiotic resistance in Europe by tackling the scientific, regulatory, and business challenges that are hampering the development of new antibiotics.”

⁴⁰ Centers for Disease Control and Prevention. “Antibiotic Resistance Threats in the United States,” 2013. www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf.

⁴¹ Boucher, HW and Talbot, GH. “10 x’20 Progress—Development of New Drugs Active Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America,” *Oxford Journal of Clinical and Infectious Diseases*, 2013.

that blocks and pumps out potentially effective antibiotics. A better understanding of these mechanisms may enable the design of more effective drugs – or of partner drugs that enhance uptake or block export of a first drug.⁴²

- **Re-sensitizing bacteria to antibiotics.** By better understanding bacterial resistance mechanisms, it may be possible to develop co-treatments that inactivate resistance mechanisms and re-sensitize microbes. The combination drug amoxicillin-clavulanate (marketed as Augmentin) works in this manner: resistant bacteria produce an enzyme that degrades the antibiotic amoxicillin, and clavulanate inhibits this enzyme.

- **Understanding persister states in bacteria.** Within the human host, a subset of bacteria adopt a poorly understood persister (or dormant) state that can resist antibiotics that kill these same bacteria when they are actively growing. The difficulty in killing persister bacteria prompts longer durations of antibiotic treatment, and results in treatment failures. If the biological basis for persistence were better understood, it might be possible to target such bacteria to make treatments shorter and more effective.

- **Searching for narrow-spectrum antibiotics.** Antibiotic drug development has often focused on broad-spectrum drugs that kill a wide range of bacteria by inhibiting a target common to all of them. New broad-spectrum antibiotics to treat these infections are increasingly difficult to find, however. Focusing on functions specific to only a narrow range of bacteria may open up the range of possible drug targets. Use of narrow-spectrum agents could also minimize the impact of antibiotic therapy on the commensal bacteria in the human skin and gut, known as the microbiome. Narrow-spectrum drugs would need to be paired with rapid diagnostics that would indicate when they are appropriate for use.

- **Targeting non-essential bacterial functions to protect patients without selecting for resistance.** It may be possible to develop drugs that protect patients by blocking disease-causing potential or pathogenicity without actually killing the bacteria. For example, a drug might block the mechanism that transfers bacterial ‘virulence factors’ into human cells; pathogens lacking these mechanisms grow poorly *in vivo*.

- **Expanding access to natural products.** The majority of antibiotics on the market, starting with penicillin, are derived from ‘natural products’ – complex molecules made by one type of microbe to kill another. Very few new natural products with antibiotic activity have been discovered in the last 30 years, however.⁴³ One of the reasons is that it has been possible to screen only the small minority of microbes that can be cultured and produce their antibiotics under laboratory conditions; the remaining microbes have been inaccessible to standard screening.⁴⁴ With new genomic tools, however, it is now becoming possible to examine DNA sequences to identify antibiotics made even by microbes that cannot readily be cultured.⁴⁵

- **Supporting early-stage chemistry for novel compound libraries.** Studies have sug-

⁴² The European Union is funding work on this area under its ND4BB program. Much more is needed and there are good opportunities for transatlantic collaboration on this topic, however.

⁴³ May, M. “Drug Development: Time for Teamwork,” *Nature*, 509: S4-S5, 2014.

⁴⁴ Baltz, R. “Antimicrobials from Actinomycetes: Back to the Future,” *Microbe*, 2: 125-131, 2007.

⁴⁵ (1) Kersten, RD, et al. “A Mass Spectrometry-guided Genome Mining Approach for Natural Product Peptidogenomics,” *Nature Chemical Biology*, 7: 794-802, 2011. (2) Yamanaka, K, et al. “Direct Cloning and Refactoring of a Silent Lipopeptide Biosynthetic Gene Cluster Yields the Antibiotic Taromycin A,” *Proceedings of the National Academy of Sciences of the United States of America*, 111: 1957-1962, 2014.

gested that conventional synthetic chemical libraries, which are the starting materials for many screens to discover new antibiotics, are not well suited to antibiotic discovery. Novel chemical approaches have been developed to create chemicals that more closely resemble natural products, and some of these chemicals have shown promise as possible antibiotics. The creation of larger, publicly available compound collections for antibiotic testing could support numerous public and private research efforts.

- **Expanding approaches that do not rely on traditional antibiotic molecules.** Possibilities include vaccination and engineered antibodies against certain microbes; quorum-sensing approaches to reducing bacterial infections; drugs that improve the human immune response; use of benign microbial populations that compete with pathogenic organisms; and use of viruses that selectively attack specific types of bacteria.

PCAST believes that U.S. investment in research and development needs to be substantially increased to address the urgent national need and to take advantage of new scientific opportunities, ranging from fundamental research to early stages of drug development. NIH currently provides approximately \$250 million in funding for research directly focused on understanding and overcoming antibiotic resistance, but these efforts need to be substantially expanded. In addition, research investments at FDA, DARPA and DTRA should be increased. DARPA, in particular, has important and growing expertise in biotechnology and an effective model for supporting out-of-the-box technology development that could propel new approaches.

We recommend that total research funding be increased by a total of \$150 million per year. To ensure accountability and monitor success, these investments should be treated as part of a distinct research portfolio whose composition is regularly reported to DNARP and whose impact can be directly evaluated.

3.2 Finding alternatives to antibiotics in animal agriculture

Another focus of research should be to devise alternatives to the use of antibiotics for nontherapeutic purposes in agriculture. Antibiotics are extensively used not only to treat sick animals, but also to prevent infection and promote animal growth. All of these uses foster the evolution of antibiotic-resistant microbes, which can spread to humans. While the magnitude of the impact of agriculture on the prevalence of resistant infections in humans still needs to be clarified, there are strong reasons to minimize the use of antibiotics in agriculture. In Section 7, we discuss recent steps that the FDA is taking to promote the judicious use of antibiotics in agriculture.

As a complement to limiting the use of antibiotics in animal agriculture, it would be valuable to develop alternatives to the use of antibiotics for growth promotion and disease prevention in livestock. Accomplishing this goal will require significant research advances.

(1) Growth promotion. The biological mechanism by which antibiotics promote growth is poorly understood and should be further investigated. Antibiotics may alter the microbial population in an animal's digestive tract (the 'microbiome') so as to allow the animal to gain

weight faster. With new tools such as genome sequencing, NIH-funded and other studies have begun to characterize the human microbiome in great detail and to chart associations with human disease. Similar studies in agriculture might suggest ways to manipulate an animal's microbial community without using antibiotics – for example, by feeding animals a 'probiotic' mixture of bacteria that alter the microbial population and the host.

(2) Disease prevention. As in the case of human health care, novel approaches to disease prevention should be pursued, particularly against bacteria in which antibiotic resistance is especially challenging. For example, many important livestock and poultry diseases are caused by viruses that, secondarily, result in bacterial infections requiring the therapeutic use of antibiotics; effective vaccines against these viral agents could substantially reduce the use of antibiotics.

USDA currently supports some research directed toward these goals through its intramural Agricultural Research Service, but substantially expanded efforts will be needed to make progress. In its report on *Agricultural Preparedness and the United States Agriculture Research Enterprise* in 2012, PCAST called for the creation of large, multidisciplinary USDA Innovation Institutes focused on emerging challenges to agriculture, supported by public-private partnerships at a Federal funding level of \$25 million per year. The President's FY15 budget contains funds to support three USDA Innovation Institutes at \$25 million per year each, including one to be focused on research on antimicrobial resistance.⁴⁶ This Innovation Institute would be an ideal home not only for basic research on antibiotic resistance, but also for research to identify alternatives to antibiotics in agriculture. The Institute should also coordinate with efforts to explore alternatives to antibiotics in medical research.

Several other agencies also have scientific expertise that could contribute to this challenge, including NIH, BARDA, and DARPA. In addition, we believe that there would be considerable interest from U.S. industry in such efforts, including in public-private partnerships. Agriculture may even be an attractive test-bed for new ideas that could be applied in human medicine, arguing for a coupling with medical research.

⁴⁶ "The Budget includes \$75 million to support three multidisciplinary institutes, with one dedicated to advanced biobased manufacturing, another to focus on anti-microbial resistance research, and the third on crop science and pollinator health. These institutes, recommended by the President's Council of Advisors on Science and Technology, will leverage the best research within the public and private sectors to create opportunities for new business ventures funded by the private sector." (Office of Management and Budget. *Fiscal Year 2015 Budget of the U.S. Government*, pg. 47. www.WhiteHouse.gov/sites/default/files/omb/budget/fy2015/assets/budget.pdf.)

Recommendation 3. Fundamental Research

(1) Expand fundamental research relevant to developing antibiotics for human healthcare and other approaches to treating bacterial infections.

The Administration should request dedicated funds for NIH and FDA to support fundamental research aimed at understanding and overcoming antibiotic resistance, and for DARPA and DTRA to support non-traditional approaches to overcoming antibiotic resistance. An appropriate funding level would be \$150 million per year over a period of 7 years, with rigorous evaluation of its effectiveness at the end of this period. Support should consist of new appropriations, rather than repurposing of existing funds.

(2) Develop alternatives to antibiotics in agriculture.

USDA should establish a multidisciplinary Innovation Institute that brings together university scientists, private companies, and USDA scientists to study antibiotic resistance and to develop alternatives to antibiotic use in agriculture, including creating opportunities for new business ventures. The Innovation Institute will require \$25 million in annual funding. Initial funding is already requested in the President's FY15 Budget.

USDA could partner with NIH to expand the scope of the Innovation Institute to include parallel questions about antibiotic resistance in humans.

USDA should develop, in collaboration with NIH and the agriculture industry, a comprehensive research and development strategy to promote the creation of alternatives to or improved uses of antibiotics in food animals, including through public-private partnerships and coordination with biomedical research.

The investments recommended above should be considered a distinct research portfolio under the National Action Plan, whose composition is regularly reported to DNARP and whose impact against measurable goals can be directly evaluated.



IV. New Antibiotics: Clinical Trials

The most expensive component of drug development is typically the Phase 2 and Phase 3 clinical trials required to prove safety and efficacy in order to register a drug for FDA approval. Moreover, clinical trials of antibiotics face special challenges that add to their cost. While clinical trials are inherently costly, there are ways to decrease their costs by (1) increasing their efficiency through improved infrastructure and (2) focusing them on patient populations in which the need is most urgent, and the effect most likely to be the greatest.

4.1 National clinical trial networks for testing antibiotics

Traditional approaches for setting up clinical trials are not well suited for testing drug candidates for treating antibiotic-resistant infections. First, the urgent need to start patients on treatment often precludes trial enrollment; treatment often must begin even before information on the identity of the pathogen is available, posing challenges for subject selection. Second, any given clinical trial site is likely to have only a few patients with the infection of interest at any one time. Third, each drug developer typically sets up a new network of sites for each clinical trial; this process can be slow and inefficient.

Individual clinical trials would become more efficient and less expensive if there existed a robust, standing national clinical trials network for antibiotic testing. Such a network would allow rapid initiation of clinical trials by commercial sponsors and academic researchers and would optimize the identification and enrollment of patients. The network should:

- incorporate state-of-the-art diagnostic tests to rapidly identify eligible patients and subsequent genomic analysis to characterize pathogens;
- develop mechanisms for broadly sharing clinical and genomic data, in order to maximize the information that can be extracted from studies; and
- allow rapid and flexible inclusion and exclusion of trial sites from the specific trials as challenges with antibiotic resistance wax and wane in geographic regions;
- effectively serve the private sector – especially, the needs of the small biotechnology firms that are conducting many of the trials for new antibiotics; and
- develop ‘platform trials’ for antibiotics, where multiple new agents from different sponsors can be evaluated concurrently (similar to some recent efforts in clinical trials in oncology).

The NIH and FDA plan to convene industry and other public and private stakeholders in late July 2014 to discuss the development of new antibacterial products. Among other topics, this meeting will discuss the requirements of a clinical trials infrastructure and consider alternative approaches. Based on input from this meeting, NIH and FDA should propose a specific plan to create a clinical trials infrastructure, including ways to ensure that financial, regulatory and logistic support are provided for the establishment of a network. It is likely that the foundations for this

infrastructure can be assembled from existing sites and networks. We estimate that the total cost for the clinical trials capability will be \$25 million to establish infrastructure and common protocols, with additional funds needed from partnerships for late stage clinical trials.

The Antibacterial Resistance Leadership Group (ARLG) launched in 2013 by the NIH's National Institute of Allergy and Infectious Disease (NIAID) might provide a strong foundation for the proposed clinical trials infrastructure. ARLG is a clinical network for the study of antibiotic resistance. NIAID hopes to expand this clinical network for the study of antibiotic resistance to integrate additional clinical sites for trial enrollment in the United States together with international sites.

4.2 Drug approval based on clinical trials in limited patient populations

The developer of a new drug candidate that can treat both antibiotic-resistant and antibiotic-sensitive infections might wish to seek initial approval only for antibiotic-resistant infections, because the benefit-risk ratio is likely to be largest in this setting and because safety and effectiveness may be demonstrated in smaller clinical trials. Approving drugs based on such trials would speed their availability to patients with antibiotic-resistant infections; there are challenges, however, associated with labeling such drugs in a manner that adequately conveys the limitations of the data supporting approval and the need for judicious use of such products only in appropriate clinical circumstances.

In PCAST's 2012 report on *Propelling Innovation in Drug Discovery, Development, and Evaluation*, we recommended the development of a new pathway for initial drug approval by the FDA (which we called 'Special Medical Use') when a candidate drug had been shown to be safe and effective in limited, defined group of patients. A 'Special Medical Use' (SMU) pathway would provide a more rapid solution for patients and companies with a potentially more rapid, albeit more limited, path to market. In particular, PCAST cited the case of drugs against antibiotic-resistant bacteria, where such drugs might be initially tested in the limited population of patients known or highly suspected to be infected with the relevant resistant pathogen.

The challenge is ensuring that drugs approved based on safety and efficacy in a limited population are not widely used in broader populations. Although physicians have the legal right to prescribe approved drugs off-label, FDA would need adequate mechanisms to discourage most such use.

FDA has noted that it is unclear whether it possesses the full legal authority to implement a full SMU pathway and it would prefer that Congress provide explicit endorsement. In advance of legislative action, however, we believe that FDA has many tools that it could use to implement aspects of an SMU pathway for antibiotics (including strong labeling, limiting prescriptions to certain trained providers, dispensing by certified institutions, and administration in specific health care settings). We urge FDA to do so. FDA should also coordinate closely with the European Medicines Agency, which appears to be proceeding in a similar direction.

Recommendation 4. Clinical Trials of New Antibiotics

(1) Establish a robust national infrastructure to support clinical trials of new antibiotics.

After convening industry and other public and private stakeholders to define the requirements for an appropriate clinical trials infrastructure, NIH and FDA should propose a plan to create such an infrastructure. We estimate the annual cost at \$25 million to establish infrastructure and common protocols, with additional funds needed from partnerships for late stage clinical trials.

(2) Develop new regulatory pathways to evaluate urgently needed antibiotics.

FDA should use existing mechanisms to facilitate approval of drugs based on demonstration of safety and efficacy in specific patients infected with antibiotic-resistant bacteria, while discouraging use in other patient populations. In parallel, the Administration should support the passage of legislation that explicitly authorizes the FDA to establish a full Special Medical Use pathway for antibiotics.



V. New Antibiotics: Commercial Development

Because bacteria steadily evolve resistance to antibiotics, a steady supply of new antibiotic therapies is needed. It is therefore deeply distressing that the development of new antibiotics has markedly declined over the past several decades. The situation is particularly serious for life-threatening Gram-negative bacteria, for which no new systematic antibiotics have been approved in 7 years. Moreover, newer antibiotics are often slight modifications of existing drugs, rather than new classes of antibiotics (each drug class typically has a unique mode of action). Most large pharmaceutical companies have abandoned antibiotic development in favor of medicines with greater potential return on investment; fewer than 5 of the top 50 pharmaceutical companies currently have significant ongoing programs to develop antibiotics. Most antibiotic development programs reside in smaller biotechnology companies. Overall, the current pipeline of antibiotic development is inadequate to combat resistance.

In sharp contrast, the current pipeline for anti-cancer therapies is brimming with hundreds of new candidate drugs. The explanation is simple: antibiotics are much less profitable than cancer drugs at current rates of reimbursement by insurance and third-party payers. Whereas effective antibiotics are typically used for a brief course and reimbursed at a low rate, cancer often requires chronic treatment and new, targeted drugs often carry prices exceeding \$100,000.

PCAST believes that there is no way to sustain a robust pipeline of antibiotic development without a major influx of private investment. This will require substantially changing the economics of drug development. The previous two sections discussed steps that can help decrease drug development costs, through fundamental research (yielding biological knowledge and chemical leads that can increase the chances of success) and increased efficiency of clinical trials (through establishment of a standing network and a focus on limited populations). *These steps alone will not sufficiently move the needle with respect to commercial investment, however.*

Major economic incentives will be necessary to substantially expand private investment in developing urgently needed antibiotics, including drugs to address evolving future needs. These incentives can come in the form of direct cost sharing for drug-development projects or increased reimbursement for successful drugs. To attract investors, incentives will need to have sufficient clarity and certainty.

In this section, we discuss four approaches that have been proposed.

None of these approaches will be easy to implement. They require new legislation to create new authorities, new appropriations, or both. Each will entail significant costs. Moreover, the measures may not be popular, because they may be viewed as benefiting pharmaceutical companies. Yet, new measures are essential. While we recognize the political and financial chal-

lenges, PCAST believes that the magnitude of the public-health problem and the necessity of stimulating private investment require that such measures be considered. Robust antibiotic development is, in significant measure, a public good; it will not happen without significant public investment.

Whatever the strategy, it will be important to ensure that public funds used to incentivize the development of antibiotics come with appropriate obligations and be properly targeted. In return for providing investment and assistance, the Federal Government should expect transparency of pricing and profits by companies, as well as measures to ensure affordability and accessibility of antibiotics to all patients who require them. In addition, any incentives should be accompanied by requirements for an antibiotic stewardship program, to prolong the utility of the antibiotic. Moreover, incentives should be limited to the development of antibiotics likely to be able to address important current or future public needs.⁴⁷

A full analysis of their economic costs, optimal structure and political feasibility of the four options is beyond the scope of this report. We recommend that the DNARP rapidly consult with stakeholders and recommend to the President a specific package of approaches to be pursued.

Before turning to the options, we elaborate on the economic challenges of commercial development of new antibiotics.

5.1 Economics of antibiotic development

The inadequate state of antibiotic development reflects a market failure: while society's need for new antibiotics is great, the economic return on developing new antibiotics is currently too low to elicit adequate private investment and innovation. PCAST discussed issues with the economics of drug development in general in its report *Propelling Innovation in Drug Discovery, Development, and Evaluation* in September 2012. The issues for antibiotic development are especially challenging.

The total capitalized cost of new therapeutic products, developed by the pharmaceutical industry, including amortizing the costs of failed projects, has been estimated at an average of \$1.2 billion, which is spent over a period of approximately 11 years.⁴⁸ According to industry observers, annual sales in the range of \$400-600 million over a period of 10 years are required to provide an adequate return for an investment of this magnitude.⁴⁹

⁴⁷ The criteria for novel antibiotics used in the Generating Antibiotic Incentives Now legislation provide an example of appropriate forward-looking criteria for new agents.

⁴⁸ DiMasi, JA and Grobowski, HG. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics*, 28: 469-479, 2007.

⁴⁹ The net present value of annual sales of \$400 million over a decade is \$1.8 billion at the point that the drug comes on the market, if one assumes net revenues equal to ~75 percent of sales and a discount rate of 10 percent; because sales are likely to start small and grow, the net present value for a drug with *average* sales of \$400 million is considerably lower. Against this return, one must weigh the cost of drug development; the present value at the time the drug comes on the market is higher than the estimated \$1.2 billion in costs because costs were incurred over the preceding decade.

Although such sales might be typical for a therapy for a chronic disease or disorder, they are not likely to be common for new antibiotics for multiple reasons. First, there is a strong and appropriate desire to preserve the lifetime of a new agent by limiting its use insofar as possible, and additional measures, beyond the current efforts, will likely be introduced to appropriately reduce antibiotic use even further. Second, the number of patients who would be appropriate candidates for treatment with a novel therapy may be limited. Third, there is a need for multiple drugs with diverse mechanisms to provide societal protection against emergence of resistance to any given class of agent; but the existence of multiple drugs would further reduce the market return for any individual drug.

To illustrate the economic issues,⁵⁰ it is helpful to consider a simplified example. Suppose that a company is deciding whether to invest in creating a novel narrow-spectrum agent for the Gram-negative *Acinetobacter*, appropriate for treating patients infected with carbapenem-resistant strains. To achieve sales of \$400 million, cited as a minimum threshold to support investment, each of the approximately 75,000 infected patients with resistant *Acinetobacter* infections identified per year globally, would need to pay \$5,300 per course (considerably higher than the cost of any antibiotic today) – assuming that it were used by every eligible patient in the world. In fact, the price would need to be considerably higher – perhaps more than \$20,000 per course – to be economically viable, because the actual number of patients taking the drug would be smaller, owing to limited access to health care worldwide and to potential competition from other drugs.

In 2012, Congress sought to increase economic incentives by including the provisions of the Generating Antibiotics Incentives Now (GAIN) Act within the Food and Drug Administration Safety and Innovation Act (FDASIA). Among its provisions, the GAIN Act guarantees five years of additional market exclusivity for antibiotics that target qualified pathogens.⁵¹ Unfortunately, the economic impact of this provision is rather limited – because the additional 5-year period runs concurrently with the patent protection of the drug, the average extension to market exclusivity is only 2 to 3 years and the sales during this period have little net present value as they occur almost three decades after the innovator begins the research project which produces the new drug.⁵² Although the GAIN Act was an appropriate step by Congress for various reasons (including its requirement that FDA provide guidance on pathogen-focused development), Government and industry experts have stated in discussions with PCAST that the GAIN Act's economic provisions have had no significant impact on pharmaceutical companies and only modest

⁵⁰ Spellberg, B and Rex, JH. "The Value of Single-Pathogen Antibacterial Agents," *Nature Reviews Drug Discovery*, 12: 963-964, 2013.

⁵¹ The act also assures that applications for such drugs will receive priority review by the FDA.

⁵² The primary value of the guaranteed-exclusivity period occurs in the event that a patent is voided. See detailed analysis in Spellberg, B, Sharma, P and Rex, JH. "The Critical Impact of Time Discounting on Economic Incentives to Overcome the Antibiotic Market Failure," *Nature Reviews Drug Discovery*, 11: 168, 2012.

www.ohe.org/publications/article/new-drugs-to-tackle-antimicrobial-resistance-analysis-of-eu-policy-options-21.cfm.

impact on small biotechnology firms. It is too early to measure directly its impact on new antibiotic development.

New mechanisms are clearly needed to incentivize the development of antibiotics.

5.2 ‘Push’ mechanisms: Direct Federal partnership in antibiotic development

One approach is to use ‘push’ mechanisms that encourage firms to invest in antibiotic development by subsidizing, in part or in whole, research and development programs for antibiotics addressing urgent public health needs. In particular, BARDA is well suited to incentivize the development of new antibiotics through innovative and flexible partnering mechanisms with industry.

BARDA was established to advance the development, manufacturing and acquisition of medical countermeasures against chemical, biological, radiological and nuclear threats, pandemic influenza, and emerging infectious diseases. Indeed, the first goal of BARDA’s 2011-2016 Strategic Plan is to facilitate the development of “medical countermeasures and platforms to address unmet public health needs, emphasizing innovation, flexibility, multi-purpose and broad spectrum application, and long-term sustainability.” BARDA has a successful track record in developing, procuring, and stockpiling medical products. To date, BARDA has invested approximately \$2.5 billion in advanced research and development of medical countermeasures against threats. Two products have already achieved licensure under the FDA’s Animal Rule (in 2012 and 2013) and BARDA anticipates that 3-5 more products may receive FDA approval by the end of 2016.

Although BARDA’s primary focus has been bioterrorism threats on the material threat agents list provided by the Department of Homeland Security (DHS), and pandemic influenza, the agency has legal authority to support advanced development for countermeasures to emerging infectious diseases. BARDA has not fully applied this authority, however; the investments in antibiotics to date have been relatively modest and have been justified primarily by security/bioterrorism considerations and not broad public health benefits.

BARDA began an antibiotic development partnership program in 2010, under which it has awarded six contracts to advance drug candidates that are typically ready for Phase 1 or 2 clinical trials. The contracts include support for development of a single drug (typical size: \$100 million total over five years) or a flexible portfolio⁵³ of drugs (approximately: \$200 million over five years). The companies typically invest an equal amount of funding from their own resources. Of these drug candidates, only a minority will likely turn into successful drugs. Based on industry averages, BARDA estimates that this fraction might be in the range of one-sixth to one-eighth. This corresponds to a total cost per successful drug (that is, amortizing failures) in the range of \$1.2-1.8 billion, with \$600-\$800 million from Federal funds.

⁵³ Under the flexible portfolio, BARDA and the drug company provide joint strategic oversight and can remove drug candidates or include new drug candidates in the portfolio, based on evolving data.

PCAST feels strongly that BARDA's antibiotic development program should be expanded beyond projects justified by security/bioterrorism considerations to include antibiotics that meet urgent public health priorities that are not traditionally defined as material threat agents. With funding of \$400 million per year for such projects, BARDA's program might yield 0.5 successful antibiotic drugs per year (that is, one every two years).

Direct Federal funding and technical support for antibiotic development has a number of advantages: (1) By substantially decreasing the direct investment required, subsidies allow developers to make a stronger business case to enter or stay involved in antibiotic research and development. (2) Upfront subsidies can be considerably smaller than equally potent market-based 'pull' incentives such as prizes or advance purchase commitments, because they entail considerably less risk. (3) Funding at this level can be targeted to encourage the pursuit of diverse approaches, including high-risk (but high societal value) approaches that might otherwise not be pursued. On the other hand, direct support for development entails selecting contractors in advance, rather than having multiple firms engage in market-based competition.

We note that the Federal Government might partner with other countries or non-profit organizations in providing subsidies for antibiotic development.

5.3 'Pull' mechanisms: Economic rewards for drug developers

Another approach is to use 'pull' mechanisms, in which expected economic rewards are increased in order to incentivize companies to invest their own funds in development. We discuss three possible mechanisms.

(1) Substantially higher reimbursement. One 'pull' mechanism is to ensure that a new antibiotic drug commands a high price in the market. In practice, this is difficult to achieve. The Federal Government does not control pricing in the private market, and it currently has only limited flexibility with respect to Federal reimbursement. Under current law, the Centers for Medicare and Medicaid Services (CMS) reimburses drugs in outpatient and inpatient settings at a defined percentage above a drug manufacturer's Average Sales Prices (ASP). By law, CMS can reimburse premium antibiotics administered by a doctor at a rate of up to ASP plus six percent. To incentivize the development of important antibiotics, Congress could increase the allowable premium. A challenge with this approach is that it is unclear that feasible increases in premiums would be adequate to drive private investment. In addition, increased reimbursement exacerbates the incentive to overuse novel antibiotics that ought to be conserved.

(2) Delinkage. Another approach that has attracted considerable recent attention is the idea of ‘delinking’ antibiotic usage from revenues. Under such schemes, a successful developer of an antibiotic that addresses an important public health need would receive a financial reward that is not directly tied to the usage of the drug. A variety of incentive models have been proposed, including user licenses, lump sum prizes, patent buy-outs, and payments to hold drugs in strategic reserve.⁵⁴ These models would provide reduced risk to potential developers (the economic reward is defined), reduced risk to users (their cost is contained), and would allow the resulting antibiotics to be managed as a strategic resource so as to preserve their effectiveness for critical uses. In addition, these models would not create incentive for a drug maker to increase sales of the antibiotic in order to make more money.

One option would be complete delinkage. In this case, a drug developer might receive from the Federal Government a one-time lump sum payment that serves as a patent buyout and reward for bringing a new antibiotic to market. The Federal Government could contract with the drug company to produce antibiotic as needed, and limit clinical use to specific circumstances and certain pre-defined conditions. Under complete delinkage, buyouts in the range of \$1 billion might be required.

Another option would involve partial delinkage, where a drug developer would receive a reward for developing the drug and would sell the drug, but would agree to certain stewardship requirements. BARDA has used such rewards successfully to incentivize the development of medical countermeasures to bioterrorism threats, encouraging companies to complete development of Phase 3 candidates by offering rewards in the range of \$400-500 million. Congress established a \$5.6 billion Special Reserve Fund to fund advance market commitments; the fund has been used to purchase 12 products for the Strategic National Stockpile and to support the advanced research and development efforts.

BARDA could create an Antibiotic Incentive Fund (AIF) to provide advance market commitments (AMC) and milestone payments as incentives for bringing a new antibiotic to market. The advance market commitment could be structured to secure the market availability of a given number of doses per year, determined by projected demand, over a given number of years, at a specified price. As a condition of receiving a payment from the AIF, the Federal Government could require industry partners to develop and implement stewardship plans and apply other considerations (e.g., patent buyouts, restricted marketing, royalty payments, pricing discounts, etc.). Incentive payments in the range of \$400 million per drug would likely be required. At one advanced drug candidate per year, this would correspond to average annual funding of \$400 million – although an AIF would be ideally structured with no-year advance appropriation (e.g., \$4 billion over ten years) to allow flexibility in when funds are spent. Assuming a success rate of 50%, such an investment might lead to an average of 0.5 new approved drugs per year (that is, one every two years).

⁵⁴ Morel, CM, and Mossialos, E. “Stoking the Antibiotic Pipeline,” *BMJ*, 340:1115-1118, 2010.

Many details remain to be worked out with the delinkage concept. One obvious challenge is how to define the characteristics of the drugs to be rewarded and the level of reward, and another is how to ensure that knowledge about a newly registered drug is expanded over time: because most agents will be registered based on limited datasets, further studies in other settings will be required and would likely need to be incentivized as well. Resolving these issues will require consensus and collaboration from multiple stakeholders. The experience of product development partnerships for neglected diseases may provide useful insight in how to commercialize drugs with relatively less lucrative markets at close-to-marginal cost pricing. Such initiatives have even brought to market drugs no longer under patent (e.g., the fixed-dose artemisinin combination for malaria) and scaled production to help meet public health needs in disease-endemic countries. Finally, we note that the cost of delinkage incentives might be shared by a global partnership involving multiple countries.

(3) Tradable vouchers to extend patent life or market exclusivity of another drug. Another approach would be to reward a successful developer of an important antibiotic with a ‘tradable voucher’ (sometimes called a ‘wildcard voucher’) that provides a short extension to the patent life (or market exclusivity period) of any drug. The developer could sell the voucher to another company with a blockbuster drug whose patent is soon to expire.

Such a voucher could be very valuable, providing a powerful incentive to potential innovators. For a mature blockbuster drug with \$4 billion in annual sales, a three-month extension would yield \$1 billion in additional sales – corresponding to profits of \$800 million, assuming margins on a mature drug of 80%. Such an incentive might elicit considerable interest from the venture capital community in launching biotechnology companies focused on new antibiotic development.

The key issue with this approach is that it would delay the transition of other drugs to generic status. Opposition to the concept may come from patients, public health advocates and manufacturers of generic drugs. Public health advocates, for example, may ask why patients taking a statin drug (or their insurers) should bear the financial burden of incentivizing antibiotic development. In addition, the total social cost of this approach is likely to be larger than some other solutions because antibiotic developers will require a fraction of the value of the tradable vouchers.

On the other hand, there are advantages to this approach. It would leave innovation decisions up to the free market. The program would not require direct appropriation from the Federal discretionary budget, although a portion of the cost would be borne by CMS as a payer. The overall cost of incentivizing antibiotic development would be spread across many different drugs, with the cost of any given three-month extension being limited.

The options above, as well as others, should be carefully analyzed with respect to the magnitude of incentive needed to have a meaningful impact on drug development, total cost, relative economic efficiency, and political feasibility.

(4) Antibiotic Usage Fee. Whatever mechanism is used, we are mindful that substantial Federal funds will be needed to provide adequate incentives. One approach to generating these funds would be to impose an Antibiotic Usage Fee – a surcharge on the cost of each antibiotic that would be committed to a dedicated fund for antibiotic incentives. An Antibiotic Usage Fee would be well justified because each use of an antibiotic contributes to the eventual development of resistance, and thus can be regarded as consuming a limited natural resource. With sales of antibiotics in human health and agriculture estimated at \$12 billion per year, a user fee of 5%, for example, would generate \$600 million that could be devoted to incentivize the development of new antibiotics, as well as to support additional actions recommended here.

Recommendation 5. The Federal Government should significantly increase economic incentives for developing urgently needed antibiotics

The DNARP should, with input from Federal experts and external stakeholders, rapidly analyze various options for attracting greater private investment in developing new antibiotics to address important health needs of today and the future, including the four options outlined in this report. The analysis should consider the impact, cost, desirability and feasibility of the options.

Informed by recommendations from the DNARP, the White House should work with the Congress to develop appropriate legislation to authorize and fund incentives aimed at increasing private sector efforts for the development of new antibiotics; with particular attention to new classes of antibiotics.

The most feasible path may comprise (1) direct Federal funding of advanced research and development for earlier stage commercial programs and (2) the establishment of an Antibiotic Incentive Fund to provide advanced market commitments and milestone payments to reward developers with later stage projects. We estimate that a total annual investment of \$800 million would be required to result in an average of one new approved antibiotic per year.



VI. Stewardship of Current Antibiotics: Human Health Care

Soon after the discovery of penicillin, studies appeared demonstrating the overuse of antibiotics by physicians.⁵⁵ In the early 1970s, reports showed that oversight by infectious-disease physicians and pharmacists could improve antibiotic prescribing patterns of primary care physicians.⁵⁶ Since then, some hospitals, particularly in academic medical centers, have pioneered antibiotic stewardship programs. *Antibiotic stewardship* refers to systematic efforts to optimize the use of antibiotics – not just reduce the total volume used – in order to maximize their benefits to patients, while minimizing both the rise of antibiotic resistance as well as adverse effects to patients from unnecessary antibiotic therapy. Stewardship involves identifying the microbe responsible for disease; selecting the appropriate antibiotic, dosing, route, and duration of antibiotic therapy; and discontinuing antibiotics when they are no longer needed. Antibiotic stewardship programs have been shown clearly to reduce the percentage of antibiotic-resistant organisms in a facility, reduce the occurrence of *C. difficile* infections, improve patient outcomes, decrease toxicity, and reduce pharmacy costs.⁵⁷

Yet, antibiotic stewardship programs are not sufficiently widespread throughout the United States. Recent surveys indicate that only 50 percent of hospitals in the United States have implemented antibiotic stewardship programs, with many community hospitals and hospitals in certain regions being less likely to have programs. Common barriers to implementation include higher priority clinical initiatives, staffing constraints and insufficient funding.^{58,59}

⁵⁵ “Abuse of Antibiotics,” *The Lancet*, 265(687): 1059-1060, 1955.

⁵⁶ (1) Kunin, CM, Tupasi, T and Craig WA. “Use of Antibiotics: A Brief Exposition of the Problem and Some Tentative Solutions,” *Annals of Internal Medicine*, 79(4): 555-560, 1973. (2) McGowan, JE and Finland, M. “Usage of Antibiotics in a General Hospital: Effect of Requiring Justification,” *Journal of Infectious Disease*. 130: 165-168, 1974.

⁵⁷ (1) White, AC, Atmar, RL, Wilson, J, et al. “Effects of Requiring Prior Authorization for Selected Antimicrobials: Expenditures, Susceptibilities, and Clinical Outcomes,” *Clinical Infectious Diseases*, 25: 230-239, 1997. (2) Singh, N, Rogers, P, Atwood, CW, Wagener, MM and Yu, VL. “Short-course Empiric Antibiotic Therapy for Patients with Pulmonary Infiltrates in the Intensive Care Unit,” *American Journal of Respiratory and Critical Care Medicine*, 163: 505-511, 2000. (3) Malani, AN, Richards, PG, Kapila, S, et al. “Clinical and Economic Outcomes from a Community Hospital’s Antimicrobial Stewardship Program,” *American Journal of Infection Control*, 41: 145-148, 2013. (4) Aldeyab, MA, et al. “An Evaluation of the Impact of Antibiotic Stewardship on Reducing the Use of High-risk Antibiotics and its Effect on the Incidence of *Clostridium difficile* Infection in Hospital Settings,” *Journal of Antimicrobial Chemotherapy*, 67(12): 2988-2996, 2012.

⁵⁸ Antibiotic stewardship functions will require dedicated staff; however, much of this funding can be offset by the expected savings in antibiotic costs. Programs are generally run by a physician and a pharmacist with subject matter expertise in infectious diseases. While many physicians and pharmacists have advanced board certification in infectious diseases, advanced certification is not a requirement to lead a successful stewardship program. Many institutions have programs that are led by hospitalists and staff pharmacists – staffing that is already available at the vast majority of institutions across the country. California is the only state with legislation (California SB 739) requiring antibiotic stewardship at acute care hospitals; it provides an excellent example of the feasibility of wide-

Most antibacterial drugs prescribed for humans are administered in outpatient settings rather than in hospitals. In ambulatory care, the vast majority of antibiotics are used for acute respiratory tract infections. Yet most respiratory tract infections are caused by viruses, against which antibacterial drugs are useless.⁶⁰ Such inappropriate use contributes directly and substantially to increased antibiotic resistance, increased adverse drug reactions, increased *C. difficile* infections, and increased cost of care.⁶¹ Antibiotics can also cause significant detrimental effects to the beneficial bacterial communities of the human body, with possible adverse long-term impacts on health; patients should not need to risk these effects in those cases, such as viral infections, where antibiotics are not useful. Inappropriate prescribing is an issue of particular importance in pediatric settings, where parents may expect physicians to prescribe antibiotics to their ailing children even when such treatment may not be appropriate.

Efforts to improve antibiotic use in ambulatory care have generally lagged behind hospital-based efforts. While various strategies have been shown to be successful, sustaining improvements without ongoing interventions have been difficult.⁶²

6.1 Advancing antibiotic stewardship

We believe one of the most effective ways to promote antibiotic stewardship in health care and community settings is to use incentives available to CMS within the Department of Health and Human Services.

Stewardship in hospitals and long-term-care facilities. In various health care settings, CMS can require adoption of an antibiotic stewardship program as a Condition of Participation (CoP)⁶³

spread implementation of antibiotic stewardship programs driven by a mandate. The response to the California experience supports the adoption of a similar antibiotic stewardship program policy throughout the United States.⁵⁹ (1) Pope SD, Dellit TH, Owens RC, and Hooton TM, Infectious Diseases Society of America, Society for Healthcare Epidemiology of America. "Results of survey on implementation of Infectious Diseases Society of America and Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship," *Infection Control and Hospital Epidemiology*, 30(1): 97-98, 2009. (2) Johannsson B, et al. "Improving Antimicrobial Stewardship: the Evolution of Programmatic Strategies and Barriers," *Infection Control and Hospital Epidemiology*, 32(4): 367-374, 2011. (3) Doron S, et al. "A Nationwide Survey of Antimicrobial Stewardship Practices," *Clinical Therapeutics*, 35(6): 758-765, 2013.

⁶⁰ (1) Barnett, M and Linder, J. "Antibiotic Prescribing for Adults with Acute Bronchitis in the United States," ID-Week-Advancing Science, Improving Care, San Francisco, CA, 2013; (2) Gonzales, R, Malone, DC, Maselli, JH, et al. "Excessive Antibiotic Use for Acute Respiratory Infections in the United States," *Journal of Clinical and Infectious Disease*, 33(6): 757-762, 2001; (3) Metlay, JP, Stafford, RS, Singer, DE. "National Trends in the Use of Antibiotics by Primary Care Physicians for Adult Patients with Cough," *Archives of Internal Medicine*, 158(16): 1813-1818, 1998.

⁶¹ Shehab, N, Patel, PR, et al. "Emergency Department Visits for Antibiotic-associated Adverse Events," *Journal of Clinical and Infectious Diseases*, 47(6): 735-743, 2008.

⁶² (1) Gerber, JS, Prasad, PA, Fiks, AG, et al. "Effect of an Outpatient Antimicrobial Stewardship Intervention on Broad-spectrum Antibiotic Prescribing by Primary Care Pediatricians: A Randomized Trial," *Journal of American Medical Association*, 309(22): 2345-2352, 2013; (2) Arnold, SR and Straus, SE. "Interventions to Improve Antibiotic Prescribing Practices in Ambulatory Care," *Cochrane Database of Systematic Reviews*, 2005.

⁶³ CMS develops a number of Conditions of Participation (CoPs) and Conditions for Coverage (CfCs) that health care organizations must meet in order to begin and continue participating in the Medicare and Medicaid programs. These health and safety standards are the foundation for improving quality and protecting the health and safety of

for the Medicare and Medicaid programs. CMS has CoPs covering many practices, such as administration of blood products and medications, ordering procedures, and infection control. The infection-control CoP changed hospital practices from being reactive (with measures deployed after the outbreak of infections) to proactive (with successful large-scale interventions that prevent serious health care-associated infections such as central line-associated bloodstream infections, surgical site infections, and the transmission of resistant pathogens from patient to patient).⁶⁴ The CoPs have proven to be an effective lever to change hospital practices broadly for all patients. A CoP for antibiotic stewardship could be similarly effective.^{65,66}

CoPs for antibiotic stewardship should be developed not only for hospitals, but also for long-term care facilities. Because such facilities accept medically complex patients, often on transfer from acute care hospitals, and such patients are at greater risk of having undergone antibiotic treatment, these institutions have been implicated in outbreaks of multi-drug resistant infection.⁶⁷

Stewardship in outpatient settings. In the outpatient setting, CMS should include quality measures that assess excessive or inappropriate antibiotic prescribing in PQRS. PQRS is a voluntary reporting program that helps providers assess and improve the quality of care they are giving so that patients receive the right care at the right time.⁶⁸ Inclusion of such quality measures will give physicians the opportunity to avoid the payment penalty for non-participation in PQRS

beneficiaries. CMS also ensures that the standards of accrediting organizations recognized by CMS (through a process called 'deeming') meet or exceed the Medicare standards set forth in the CoPs and CfCs.

⁶⁴ (1) Pronovost, P, Needham, D, et al. "An intervention to decrease catheter-related bloodstream infections in the ICU," *New England Journal of Medicine*, 355(26): 2725-32, 2006; (2) Huang, SS, Septimus, E, Kleinman, K, et al. "CDC Prevention Epicenters Program," <http://www.cdc.gov/HAI/epiCenters/Index.html>; (3) AHRQ, "Targeted versus universal decolonization to prevent ICU infection," *New England Journal Medicine*, 368(24): 2255-65, 2013.

⁶⁵ The CoP should include the requirements that (1) a specific person or person(s) is designated as the antibiotic stewardship officer to develop and implement policies governing appropriate use of antibiotics, (2) the antibiotic stewardship officer(s) must develop a system for identifying areas for improvement in antibiotic use, implementing interventions to improve use, and measuring and reporting on antibiotic use within the institution, and (3) the chief executive officer and medical staff must ensure that the institution-wide quality assurance and training programs address problems identified by the antibiotic stewardship officer. Interpretive guidance for these requirements for inclusion in the State Operation Manual should be developed by CMS in conjunction with subject matter experts, including the Centers for Disease Control and Prevention and other relevant stakeholders (e.g., Society for Healthcare Epidemiology of America, Infectious Diseases Society of America, Pediatric Infectious Disease Society, Society of Infectious Diseases Pharmacists, and American Society of Health System Pharmacists).

⁶⁶ Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS), Society for Healthcare Epidemiology of America, Pediatric Infectious Diseases Society. "Policy Statement on Antimicrobial Stewardship- Special Topic Issue: Antimicrobial Stewardship," *Infection Control and Hospital Epidemiology*, 33(4): 322-327, 2012.

⁶⁷ Munoz-Price, LS. "Long-Term Acute Care Hospitals," *Clinical Infectious Diseases*, 49: 438-443, 2009.

⁶⁸ All physicians who participate in Medicare will also be subjected to the Value Based Payment Modifier Program by 2017. CMS will provide comparative performance information to participants and a portion of physician reimbursement will be based upon these quality metrics rather than volume.

by reporting on these measures.⁶⁹ Where applicable, the antibiotic-reporting module should be mandatory.

Measuring antibiotic usage and resistance in health care facilities. To improve the use of antibiotics in health care, it will be important to aggregate existing data on both antibiotic use and resistance. The United States has lagged behind much of the developed world in collecting antibiotic use and resistance (AUR) surveillance data.⁷⁰ U.S. public health infrastructure currently lacks a systematic means to gather AUR information from individual facilities, quantify national usage patterns, correlate usage patterns with resistance, and facilitate comparisons across facilities to drive quality improvement decisions locally and to inform public health interventions regionally.⁷¹

The ideal platform for gathering AUR information is CDC's National Health Care Safety Network (NHSN). NHSN has recently created a *voluntary* AUR module for hospitals.⁷² In the FY 15 President's budget, CDC has proposed a \$14 million increase for NHSN activities that would support AUR reporting through NHSN for hospital settings. Data from this AUR module should be the basis for quality measures that are reported on Hospital Compare.⁷³ These quality measures on antibiotic use and antibiotic resistance reporting should be ready for submission to the consen-

⁶⁹ A penalty of 1.5 percent, growing to 2.0 percent beginning in 2016, is scheduled to be introduced in 2015 for failure to participate in PQRS.

⁷⁰ The European Union has made great strides with a system to evaluate regional antibiotic consumption, evaluation of inter-country differences, feedback of data to participating member states, and provision of public access to information on antibiotic consumption (Vander Stichele, RH, Elseviers, MM, Ferech, M, Blot, S, Goossens, H, and the ESAC Project Group. "Hospital Consumption of Antibiotics in 15 European Countries. Results of the ESAC Retrospective Data Collection (1997-2002)," *Journal of Antimicrobial Chemotherapy*, 58(1): 159-67, 2006). The European Centre for Disease Prevention and Control (ECDC) collects data on antibiotic consumption from twenty-nine European Union and European Economic Area countries through the European Antibiotic Resistance Surveillance Network (EARS-Net) and the European Surveillance of Antimicrobial Consumption Network (ESAC-Net). Additional examples of effective antibiotic use surveillance systems include the Central Asian and Eastern European Surveillance on Antimicrobial Resistance (CAESAR), and the Canadian Antimicrobial Resistance Alliance (CARA). These systems have used comparative data to improve antibiotic use over time and have tracked resistance trends in attempts to limit the spread of a variety of multi-drug resistant organisms.

⁷¹ Fridkin, SK and Srinivasan, A. "Implementing a Strategy for Monitoring Inpatient Antimicrobial Use Among Hospitals in the United States," *Journal of Clinical and Infectious Disease*. 58(3): 401-6, 2014.

⁷² To participate in this module, facility personnel responsible for reporting data to NHSN must coordinate with their pharmacy and/or laboratory information software providers to configure their systems to enable the generation of standard formatted file(s) to be imported into NHSN. The format provided for data submission follows the Health Level (HL7) Clinical Document Architecture (CDA). Manual data entry is not available. Therefore, implementation is contingent upon laboratory, pharmacy and surveillance information system vendors providing compatible reporting architecture. (It is likely that some facilities that do not have an electronic health record or laboratory and pharmacy information systems, e.g., some small critical-access hospitals, will need to be exempted.) It will also be necessary to boost the capacity of NHSN infrastructure to handle this large influx of data.

⁷³ (1) Ibrahim, OM and Polk, RE. "Benchmarking Antimicrobial Drug Use in Hospitals," *Expert Review of Anti Infective Therapy*, 10(4): 445-57, 2012; Polk, RE and Hohmann, SF, "Benchmarking Risk-adjusted Adult Antibacterial Drug Use in 70 US Academic Medical Center Hospitals," *Journal of Clinical and Infectious Disease*, 53(11): 1100-10, 2011; (2) MacDougall, C and Polk, RE. "Variability in Rates of Use of Antibacterials among 130 US Hospitals and Risk-Adjustment Models for Interhospital Comparison," *Journal of Infectious Control and Hospital Epidemiology*, 29(3): 203-11, 2008.

sus body entity for endorsement and implementation consideration by 2017. These are necessary steps, as is rule-making, in order to achieve nation-wide mandatory implementation in hospitals by 2020.

Obtaining data on antibiotic usage in ambulatory settings. Ambulatory settings account for more than 50 percent of antibiotic use in humans. The United States has no public health infrastructure to collect such information, but commercial vendors collect proprietary data from sources such as drug-purchase information, drug claims and charge data, and commercial pharmacy orders. (Currently, the most extensive data about U.S. usage are available from IMS Health, which creates estimates based on sampling more than 70 percent of U.S. prescriptions. Similarly, commercial data are available for use in other countries.) When available, such data have proven valuable for comparing outpatient prescribing practices across all 50 States and benchmarking relative to other countries.⁷⁴ Although the cost of these data is relatively modest, CDC has not always had funds to purchase these data; at least \$4 million should be included in CDC's budget to ensure ongoing collection of this data and to expand data collection and analysis to other areas.

Using funding requirements to drive antibiotic stewardship. In addition to using requirements related to CMS funding, Federal agencies should require implementation of antibiotic stewardship programs as a condition for receiving Federal funding for health care delivery, including in community health care centers. Federal agencies should also provide technical assistance for the implementation of stewardship programs.

Federal Government should lead by example. The United States government should lead by example with respect to antibiotic stewardship and the systematic collection of data on antibiotic use and resistance. In particular, hospitals and other health care delivery facilities within VA and DoD should report to the AUR module of NHSN. CDC should work with VA and DoD to define the steps and resources needed for routine data submission.

All health care delivery facilities operated by the Federal Government, including the over 200 hospitals run by DoD, HHS, VA, and the Indian Health Systems, should work with CDC to develop and implement antibiotic stewardship programs that meet the same criteria as non-Federal institutions. Federal agencies and departments supporting health care facilities in these efforts should report annually to DNARP on their progress towards eliminating inappropriate prescription of antibiotics. Federal agencies should also move towards mandatory implementation of antibiotic stewardship programs as a requirement for receiving Federal assistance for community health centers.

Research on improving stewardship programs. In addition, increased research is needed on how to design and implement the most effective antibiotic stewardship programs for both in-

⁷⁴ (1) Suda, KJ, and Hicks, LA. "Trends and Seasonal Variation in Outpatient Antibiotic Prescription Rates in the United States, 2006-2010," *Antimicrobial Agents and Chemotherapy*, 2014; (2) Hicks, LA, Taylor, TH Jr and Hunkler, RJ. "U.S. Outpatient Antibiotic Prescribing, 2010," *New England Journal of Medicine*, 368(15): 1461-1462, 2013.

patient and ambulatory care settings. Interdisciplinary insights from behavioral economics, cognitive psychology, sociology and other fields are likely to shed light on which types of mechanisms will best engage physicians, patients and the public at large in promoting judicious use of antibiotics, as well as in devising creative new mechanisms. This work should include determining approaches to facilitate the appropriate use and interpretation of rapid point-of-care diagnostics in clinical practice. NIH, CDC, the Agency for Health Care Research and Quality, CMS, and the Patient-Centered Outcomes Research Institute, as well as the VA and DoD, should consider support for such research. In addition, collaborative sharing among like-minded institutions could accelerate the process of continuous quality improvement and should be supported as well.

Patient education. Efforts to improve antibiotic stewardship should include education and steps to address the social and behavioral factors that drive the demand for and inappropriate prescribing of antibiotics. The CDC has supported efforts to educate patients and the general public regarding the threat of antibiotic resistance related to the inappropriate use of antibiotics such as for the treatment of viral infections.

6.2 Rapid point-of-care diagnostics

Rapid and accurate diagnosis of bacterial infections is critical both to promote optimal patient outcomes (lower adverse events, shorter hospital stays, and better long-term prognoses) and reduce the selection of antibiotic-resistant organisms. Yet, the results for most currently available diagnostics are not available in sufficient time to inform treatment decisions in outpatient settings, where most antibiotics are prescribed, as well as in many hospital settings where acute illness requires empiric antibiotic selection before relevant information is available.

Technological breakthroughs, driven by advances in genomics, can provide far more rapid means of identifying bacteria, based on detecting their DNA, RNA, and proteins, and identifying the presence of specific resistance elements.⁷⁵ Companies such as Cepheid and Nanosphere have recently obtained regulatory approval in the United States and Europe for DNA-based detection of pathogens such as MRSA, vancomycin-resistant *Enterococcus* (VRE), and rifampin-resistant TB (which often predicts multi-drug resistance). Research and development focused on even more general approaches shows promise. These high-technology solutions have only just begun to enter the hospital setting in developed countries, in part due to cost, time, and resource considerations. This progress is encouraging and the adoption of these solutions should be strongly encouraged.

Still, antibiotic stewardship would be substantially advanced by the development and widespread use of extremely inexpensive, rapid diagnostics available in outpatient settings that could provide accurate and timely information on the infecting pathogen, including whether it

⁷⁵ Martinez, RM, et al. "Molecular Analysis of *Lactobacillus* spp. Diversity in Clinical Specimens Associated with Disease," *Journal of Clinical Microbiology*, 52(1): 30-36, 2013.

is bacterial, and its resistance profile. Ideally, tests are needed that can accurately predict the need (or lack of need) for specific antibiotics in a substantial fraction of patients with otherwise non-specific clinical syndrome. Pressing needs include:

- In the United States, respiratory tract infections. To inform the prescribing decision, answers should ideally be available within 30 minutes.
- Globally, tuberculosis (TB). Because current tests for antibiotic resistance in TB often take weeks, patients frequently return home with ineffective antibiotics, during which time resistant bacteria may spread. Diagnostics that could determine antibiotic sensitivity within two hours, while challenging to create, would have a transformative impact.^{76,77}

The Federal Government should take steps to accelerate the development and adoption of such diagnostics. Prize incentives could be an effective tool. For example, particular prizes might be established for diagnostics for RTIs and TB that achieve specified performance goals.⁷⁸

FDA should also take steps to prioritize applications for diagnostic tests to detect resistant pathogens and streamline the approval process.⁷⁹ Finally, funds should be allocated for clinical validation studies.⁸⁰

⁷⁶ The recently developed Xpert MTB/RIF test provides an important step toward this goal; it detects DNA from the TB microbe and tests for resistance-conferring mutations in a one specific gene (rpoB) conferring resistance to the antibiotic rifampicin.

⁷⁷ This is a challenge due to the slow growth rate of *Mycobacterium tuberculosis*. Novel approaches, however, have recently been proposed for detecting responses indicating sensitivity or resistance before cells have even divided. (Barczak AK, et al. "RNA Signatures Allow Rapid Identification of Pathogens and Antibiotic Susceptibilities," *Proceedings of the National Academy of Science*, 2012.)

⁷⁸ The importance of such prizes was recently shown by the decision by the United Kingdom, which announced that one of its newly created Longitude Prizes (worth £10 million or approximately \$17 million) will be directed toward improved diagnostic test for bacterial infections. (Gibney, E. "Antibiotic resistance focus of UK Longitude Prize," *Nature News Blog*, June 26, 2014. <http://blogs.nature.com/news/2014/06/antibiotic-resistance-focus-of-uks-longitude-prize.html>.)

⁷⁹ For example, FDA could increase the efficiency of its review processes for diagnostics, with applications for rapid diagnostics reviewed concurrently for 510(k) approval and CLIA waiver.

⁸⁰ Many tests that perform well under ideal laboratory conditions fail with real-world clinical specimens. Studies that validate the utility and cost savings of rapid diagnostic tests in the clinical workplace would help facilitate the adoption of these tests by clinicians and laboratory directors, as well as their reimbursement by third party payers.

Recommendation 6. Improving Stewardship of Existing Antibiotics in Healthcare

(1) CMS should use reimbursement incentives to drive antibiotic stewardship.

(1) Stewardship programs in hospitals and long-term care facilities. By the end of 2017, CMS should have Federal regulations (Conditions of Participation) in place that will require U.S. hospitals, critical access hospitals, and long-term care and nursing home facilities to have in place robust antibiotic stewardship programs that adhere to best practices, such as those contained in the CDC Core Elements for Hospital Antibiotic Stewardship Program recommendations. Similar requirements should be phased in rapidly for other settings including long-term acute care hospitals, other post-acute facilities, ambulatory surgery centers, and dialysis centers.

(2) Antibiotic use in outpatient settings. CMS should expand the Physician Quality Reporting System (PQRS) to include quality measures that discourage inappropriate antibiotic use for non-bacterial infections, such as respiratory tract infections. Such measures should be developed in conjunction with subject matter experts from CDC and other relevant stakeholders.

(3) Gathering data on antibiotic use and resistance. CMS should include in the Inpatient Quality Reporting program and reporting on Hospital Compare quality measures based on data reported by healthcare facilities to the National Healthcare Safety Network (NHSN) Antimicrobial Use and Resistance (AUR) module. Such quality measures should be ready for submission to the consensus body entity for endorsement by 2017, and implementation consideration through the Measure Application Partnership by 2018. These are necessary steps, as is rule-making, in order to achieve mandatory nation-wide implementation in hospitals by 2020. CMS should also include such measures as value-based purchasing metrics in future years. CDC, in consultation with its Federal partners and private and public healthcare stakeholders, should develop risk stratification models for benchmarking of data reported to the AUR module. Finally, HHS should ensure that annually CDC has the budget needed to purchase commercial data on drug purchases and other outpatient prescribing practices.

(2) The Federal Government should use funding requirements to drive antibiotic stewardship. Federal agencies should require implementation of antibiotic stewardship programs as a condition for receiving Federal funding for healthcare delivery, including in community healthcare centers. Federal Agencies should also provide technical assistance for the implementation of stewardship programs.

(3) The Federal Government should lead by example in antibiotic stewardship in its own healthcare facilities. Healthcare delivery facilities operated by the Federal Government, including the over 200 hospitals run by DOD, HHS, and VA, should (1) work with CDC to develop and implement antibiotic stewardship programs, and (2) report to the Antimicrobial Use and Resistance (AUR) module of the National Healthcare Safety Network (NHSN). Federal agencies and Departments supporting healthcare facilities should report annually to DNARP on their progress towards eliminating inappropriate prescription of antibiotics.

(4) Prizes for the development of breakthrough diagnostics. HHS should create Global Challenge Inducement Prizes for the development of rapid, inexpensive, and clinically relevant diagnostics that can substantially improve therapy in outpatient settings (such as respiratory tract infections and tuberculosis), with criteria to be developed jointly by NIH, CDC, and FDA. Prizes might be in the range of \$25 million each, supported by Federal funding with additional funding potentially from foundations or other nations.



VII. Stewardship of Current Antibiotics: Animal Agriculture

Antibiotics are used extensively in animal agriculture.⁸¹ While antibiotics are typically used to treat animals with an active infection, some use aims to prevent infection or to promote animal growth. Disease prevention in animals is a laudable goal. Prevention of infection in animals can improve food safety for humans, and growth promotion assists the U.S. agriculture industry in meeting the food needs of the United States and the unprecedented worldwide demand for protein from animal sources, especially in the developing world.

The benefits of antibiotic use in animal agriculture, however, must be weighed carefully against the serious potential risks to human health posed by antibiotic resistance. All uses of antibiotics – whether in human or animal populations – promote the emergence and spread of antibiotic resistance by selecting for microbes able to grow well despite the presence of antibiotics. Notably, treatment with one antibiotic can select for resistance not only to that antibiotic but also to other unrelated antibiotics – because bacteria often become resistant through the acquisition of transmissible genetic elements, such as plasmids, that carry several resistance genes.⁸² It is therefore important that antibiotics be used judiciously in animal agriculture, and especially so for those antibiotics that are critically important for human medicine.⁸³

7.1 Links between antibiotic resistance in animals and humans

Substantial evidence demonstrates that use of antibiotics in animal agriculture promotes the development of antibiotic-resistant microbes in animals and that retail meat can be a source of microbes, including antibiotic-resistant microbes.⁸⁴ Moreover, antibiotic resistance can spread

⁸¹ (1) Food and Drug Administration. "Estimates of Antibacterial Drug Sales in Human Medicine," 2012. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm261160.htm>; (2) Food and Drug Administration. "Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals," 2009. www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM231851.pdf; (3) Food and Drug Administration. "Estimate of Antibacterial Drug Sales for Use in Humans," 2012.

⁸² For example, researchers at USDA and collaborators have shown that antibiotics in feed given to swine cause a significant increase in the abundance of resistance genes for antibiotics not included in the feed. (Looft, T, et al. "In-feed Antibiotic Effects on the Swine Intestinal Microbiome," *Proceedings of the National Academy of Sciences of the United States of America*, 2012.)

⁸³ These include fluoroquinolones, macrolides, and third- and fourth-generation cephalosporins. Currently several classes of antibiotics do not have veterinary equivalents, and the WHO has recommended that these (carbapenems, lipopeptides and oxazolidinones) and any new class of antimicrobials developed for human therapy not be used in animals, plants, or aquaculture. (World Health Organization. "Critically Important Antimicrobials in Human Medicine," 2011. http://apps.who.int/iris/bitstream/10665/77376/1/9789241504485_eng.pdf.)

⁸⁴ In 2011, retail chicken was contaminated with *Enterococcus* spp (90.2 percent); *E.coli* (71 percent); *Campylobacter* (45.7 percent) and *Salmonella* (12 percent). Moreover, 22.4 percent of *Campylobacter jejuni* were resistant to quinolones and 48.3 percent to tetracyclines. In addition, crops may be fertilized with animal manure that may

between microbes (through the transfer of DNA elements, such as plasmids, between species) and antibiotic-resistant microbes can spread from animals to people who come into contact or close proximity with them. For example, poultry workers in Maryland and Virginia have been reported to be much more likely to be colonized by gentamicin-resistant *E. coli* and are at a higher risk of infection by multi-drug resistant *E. coli* than residents of the community surrounding the poultry operation.⁸⁵ A survey of over 900 adults in Wisconsin and Minnesota found that drug-resistant *E. coli* bacteria isolates present in humans were similar to those in poultry meat, whereas drug-susceptible *E. coli* bacteria isolates were not.⁸⁶ A study of veterans in rural Iowa reported that the frequency of resistant *Staphylococcus aureus* was 88% higher among veterans living within one mile of a high-density swine-feeding operation.⁸⁷ As we note in the citations, while suggestive, these studies have important limitations.

While it is clear that agricultural use of antibiotics can affect human health, what is less clear is its relative contribution to antibiotic resistance in humans compared to inappropriate or over-use in health care settings. This uncertainty is largely due to difficulties in tracing precisely the origins and spread of specific resistant microbes, and more fundamentally, the transmission and spread of specific resistance genes in microbial communities. It also reflects a gap in our understanding of the complexity of resistance across different species and the environment.

Advances in genome analysis, however, are making feasible rigorous studies and surveillance to trace the provenance of resistant strains.⁸⁸ One recent study of over 200 livestock workers strongly suggested that methicillin and multidrug resistant *Staphylococcus aureus* (MRSA) can be transmitted (shown to be present in nasal swabs) from livestock to workers.⁸⁹ Another study

contain antimicrobial-resistant organisms. Multiple outbreaks of *E. coli* O157:H7 associated with agricultural produce were traced to contact between fresh produce and manure (Food and Drug Administration, "NARMS [National Antimicrobial Resistance Monitoring System] Retail Meat Report 2011," 2011. <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm334828.htm>).

⁸⁵ Price, LB. "Elevated Risk of Carrying Gentamicin-Resistant *Escherichia coli* among U.S. Poultry Workers," 2007. www.jhsph.edu/news/news-releases/2007/price-poultry-workers.html. The authors of this study note its small sample size (16 poultry workers and 33 community referents).

⁸⁶ Johnson, JR, et al. "Antimicrobial Drug-resistant *Escherichia coli* from Humans and Poultry Products, Minnesota and Wisconsin, 2002-2004," *Emerging Infectious Diseases*, 13(6): 838-846, 2007. The similarity of drug-resistant human isolates to poultry isolates surprisingly applied also to the isolates from vegetarians. The authors speculate that this is due to the spread of drug-resistant *E. coli* through the human population, but "cannot exclude the possibility that other foods or nonfood reservoirs might yield even closer similarities to drug-resistant human isolates."

⁸⁷ Carrel, M, et al. "Residential Proximity to Large Numbers of Swine in Feeding Operations is Associated with Increased Risk of Methicillin-resistant *Staphylococcus aureus* Colonization at Time of Hospital Admission in Rural Iowa Veterans," *Infection Control and Hospital Epidemiology*, 35(2), 2014. We note that the strength of the evidence was limited, with a p-value of 0.024 before any correction for multiple hypothesis testing.

⁸⁸ Andersson, DI and Hughes, D. "Microbiological Effects of Sublethal Levels of Antibiotics," *Nature Reviews*, 12: 465-478, 2014.

⁸⁹ Rinsky, JL, et al. "Livestock-associated Methicillin and Multidrug resistant *Staphylococcus aureus* is Present among Industrial, Not Antibiotic-free Livestock Operation Workers in North Carolina," *PloS ONE* 8(7): e67641, 2013. The study "did not observe *S. aureus* strain concordance between workers and household members. How-

demonstrated the power of whole-genome sequencing for understanding the relationship between antibiotic resistance in humans and in livestock: by analyzing MRSA from animals and humans across 19 countries and 4 continents, it showed that a strain that originated as a susceptible strain in humans spread to livestock, where it acquired methicillin resistance, and then migrated back to humans as a resistant but less virulent strain.⁹⁰ Similarly, recent genomic work has indicated that hospital-adapted, multidrug resistant enterococci, including vancomycin-resistant *Enterococcus* (VRE), originated from animal sources, emerging around the same time as the introduction of antibiotics about 70 years ago.⁹¹ Another study, however, used whole genome sequencing of 200 isolates over 22 years to examine a link between *Salmonella Typhimurium* in humans and cattle in Scotland, and found limited transmission of the bacterium and its resistance genes between animal and human populations.⁹² Rather, the resistance genes seem to have been maintained separately in the human and animal populations over that time. As these recent studies show, genomic data is providing a detailed picture of transmission patterns. With adequate data, it should be possible to understand the relationship between agricultural use and human health.

Although knowledge in this area is still incomplete, it is clear that at least some drug-resistant pathogens have evolved under selective pressure from antibiotic use in agriculture and may have contributed significantly to resistance in clinical settings. A national strategy to reduce the emergence and incidence of antibiotic resistance must therefore include substantial changes in the use of antibiotics in agricultural settings, in order to preserve antibiotic utility in human medicine. In addition, antibiotic resistance also limits the therapeutic effectiveness of antibiotics in animals themselves; this further supports the need to reduce resistance in animal agriculture.

7.2 Recent FDA actions

Building upon steps taken over the past two decades,⁹³ the FDA has recently taken actions to promote the judicious use of medically important antibiotic drugs in livestock to protect public

ever, relatively few household members participated in this study and consequently this finding should be interpreted with caution.”

⁹⁰ Price, LB, et al., “*Staphylococcus aureus* CC398: Host Adaptation and Emergence of Methicillin Resistance in Livestock,” *American Society for Microbiology*, 3(1), 2012.

⁹¹ Lebreton, F, et al. “Emergence of Epidemic Multidrug-Resistant *Enterococcus faecium* from Animal and Commensal Strains,” *mBio*, 4(4), 2013. Comparative analysis of genomic data from the first VRE from an animal source detected in the United States (Donabedian, SM, et al. “Characterization of Vancomycin-Resistant *Enterococcus faecium* Isolated from Swine in Three Michigan Counties,” *Journal of Clinical Microbiology*, 48(11): 4156-4160, 2010) suggested that its arrival was connected to international trade of livestock with Europe, where the use of antibiotics in animal feed including avoparcin, chemically similar to vancomycin, was historically widespread.

⁹² Mather, AE, et al., “Distinguishable Epidemics of Multidrug-resistant *Salmonella* Typhimurium DT104 in Different Hosts,” *Science*, 343: 1514-1517, 2013.

⁹³ The steps include: requiring that veterinary oversight of all newly approved antibiotics in the late 1980s; establishing NARMS in 1996; prohibiting the off-label use of fluoroquinolones and glycopeptides in animal agriculture in 1997; establishing a framework for assessing antimicrobial resistance risks as part of drug approval (Guidance #152) in 2003; and withdrawing enrofloxacin for use in poultry in 2005.

health.⁹⁴ The FDA has released two Guidances for Industry (GFI #209 and #213) that propose phasing out the use of medically important antibiotics in food animals for production purposes (e.g., to enhance growth or improve feed efficiency), and to ensure that licensed veterinarians oversee other uses of such drugs (to treat, control, or prevent specific diseases).⁹⁵ Before the expanded role for licensed veterinarians can begin, FDA still must finalize revisions to the Agency's Veterinary Feed Directive (VFD) regulation to improve the efficiency of the VFD program and facilitate the process of bringing the use of medically important antibiotics in animal feed under the oversight of licensed veterinarians.

The FDA guidances ask animal-drug companies to voluntarily change the labels on their drugs by either withdrawing them from animal use completely or by withdrawing claims that the drugs can be used for growth promotion. The initial response by the pharmaceutical industry is encouraging. All 26 animal-drug companies affected by Guidance #213 have agreed to comply with these voluntary changes. Importantly, once the animal-drug companies change the labels it will become *illegal* to use the drugs for growth promotion. The drugs will need to be administered under a veterinarian's order for the purposes of either disease prevention or disease treatment.

As the FDA framework is rolled out, there is an urgent need for communication and educational strategies to ensure that livestock and poultry producers: (1) understand the framework, guidances and rationale; (2) are best able to comply with these changes; and (3) are best able to adopt antibiotic stewardship programs to guide new production practices. This will require nuanced attention to the diversity of operations in U.S. agriculture (ranging from large and intensive poultry and hog production systems to numerous smaller beef cattle operations) that differ in their levels of sophistication, production practices, and use of animal health and veterinary services, and in how they receive and use information. Farmers will need information from

⁹⁴ In 2003, FDA issued Guidance for Industry #152 (*Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern*), which stated: "Prior to approving an antimicrobial new animal drug application, FDA must determine that the drug is safe and effective for its intended use in the animal...This document focuses on the concern that the use of antimicrobial new animal drugs in food-producing animals will result in the emergence and selection of antimicrobial resistant food-borne bacteria which impact human health adversely." GFI #152 presented one risk assessment approach that industry could use to evaluate the microbial food safety of antibiotic new animal drugs when industry applied for new drug approval. Since at least 2003, FDA has not approved any new antibiotics with growth promotion on their labels because of the concern that growth-promotion use could lead to a safety concern.

⁹⁵ Guidance #209 (*The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals*) established two voluntary principles: (1) The use of medically important antibiotic drugs in food-producing animals should be limited to uses that are considered necessary for assuring animal health (as opposed to growth promotion); and, (2) The use of medically important antibiotic drugs in food-producing animals should include veterinary oversight or consultation. Together, these principles help provide a framework for the voluntary adoption of practices to ensure the appropriate or judicious use of medically important antibiotic drugs. Guidance #213 (*New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligned Product Use Conditions with GFI #209*) provides procedures whereby makers of medically important antibiotics can voluntarily change the drug's label to (1) phase out claims for growth promotion and (2) establish indications for therapeutic use in food-producing animals. This Guidance triggers a change from over-the-counter (OTC) antibiotic access to prescription-based access, based on changes to FDA's Veterinary Feed Directive (VFD).

trusted sources that is both timely and accurate. Fortunately, the USDA's Cooperative Extension Service has a long tradition of working closely with farmers. The Cooperative Extension Service has a well-established infrastructure in place, a presence in every U.S. county, and has been a trusted source of information and educational programs over the last century. Other USDA agencies such as the Animal Plant Health Inspection Service (APHIS) could also be used as a trusted source of information.

7.3 Assessing the impact of the FDA framework

FDA's new framework is an important step, but it will be important to see how these voluntary changes actually impact antibiotic use and stewardship in agriculture. For example, some have expressed concern that the FDA guidances are insufficient because current antibiotic usage intended for growth promotion might be redesignated as intended for disease prevention. We note, however, that such redesignation by veterinarians would be unethical and illegal.

One test of whether the FDA guidances are effective will be whether there is a decrease in the overall sales of medically important antibiotics in animal agriculture corresponding to the elimination of their use in growth promotion. As the new FDA framework is rolled out over the next 3 years, it will therefore be essential to monitor changes in the sale of antibiotics in agriculture, especially for medically important antibiotics. FDA is required by the Animal Drug User Fee Amendments of the Federal Food, Drug, and Cosmetic Act to require sponsors of antibiotic drug products for food-producing animals to report the quantities of drugs distributed domestically and exported, as well as to provide a listing of the target animals specified on the labels. The FDA is also required to make annual summaries of the reported information publicly available, while taking steps to protect confidential business information.⁹⁶ FDA and USDA should work with the animal agriculture industry to collect more detailed data that will better allow an assessment of the impacts of the new guidances on use practices and resistance trends over time.

The ultimate goal is to decrease antibiotic resistance in both humans and animals. Realistically, it will be difficult to rigorously attribute changes in human antibiotic resistance patterns to changes in agricultural use – at least until much better surveillance systems are in place and until the flow of antibiotic resistance between reservoirs is much better understood. Elsewhere in this report (see Section 2), PCAST recommends the establishment of a national capability for microbial surveillance, including surveillance projects related to agriculture. This capability will facilitate collecting the types of data that should ultimately provide a deep understanding of the relationship between antibiotic resistance in agriculture and humans.⁹⁷

In the meantime, a combination of data on sales, data on resistant bacteria in food from NARMS, and representative information about antibiotic usage at the farm level, collected in an

⁹⁶ Food and Drug Administration. "2009 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals," 2009.

<http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM231851.pdf>.

⁹⁷ For example, these data can be used to attribute certain plasmids and genes to specific food animal reservoirs in order to guide agricultural interventions to the most appropriate locations.

appropriate manner, should help assess the impact of the new guidances. We urge FDA to work with USDA and CDC to develop such a comprehensive approach to gathering information and assessing progress.

If the FDA guidances are ultimately not effective in mitigating the risk of antibiotic resistance associated with antibiotic use in farm animals, FDA should take additional measures to protect human health.

Recommendation 7. Limiting the Use of Antibiotics in Animal Agriculture

PCAST strongly supports FDA's new Guidances 209 and 213, designed to promote the judicious use of antibiotics in agriculture.

(1) FDA should proceed vigorously with the implementation of these guidances, including completing its rulemaking to update the language of the Veterinary Feed Directive.

(2) USDA, through its Cooperative Extension Service, should establish and lead a national education and stewardship program to assist farmers, ranchers, and animal agriculture producers across the United States in complying with these FDA guidances. USDA should also work to ensure that information is distributed in an effective and timely manner to licensed veterinarians, clarifying veterinarians' new roles in overseeing the use of antibiotics.

(3) FDA should assess progress by monitoring changes in total sales of antibiotics in animal agriculture and, where possible, in usage of such antibiotics; and by developing and undertaking studies to assess whether decreases are observed in antibiotic resistance among farm animals.

If the FDA guidances are not effective in mitigating the risk of antibiotic resistance associated with antibiotic use in animal agriculture, FDA should take additional measures to protect human health.



VIII. International Cooperation

While the United States must take decisive steps to combat antibiotic resistance, the scope of the challenge will require global cooperation and solutions across the developed and developing world. As a major funder of global health, the United States has significant influence on global health policy and agenda setting. The United States should work with its international partners, as well as non-governmental organizations, to develop frameworks and projects to advance surveillance, reporting, research, antibiotic stewardship, and development of new technologies, vaccines, and antibiotics.

It will be especially important to strengthen surveillance for antibiotic resistance around the globe, because resistant bacteria spread rapidly across borders: the United States will not be immune, for example, to the brewing epidemic of XDR-TB arising in other countries. While there are a number of international resistance-surveillance networks, they are poorly coordinated with respect to standards for data collection, analysis, and reporting. Moreover, there exist collections of clinical isolates around the world, including in resource-poor settings, that are not being analyzed. The network of high-quality reference laboratories established by CDC in partnership with NIH, recommended above could play a key supporting role in international surveillance efforts. In addition to surveillance, mechanisms to gather information about global usage of antimicrobials will also be important.

International organizations such as WHO, the World Organization for Animal Health (OIE), and the Food and Agriculture Organization (FAO) are uniquely positioned to convene international stakeholders and oversee the development of global plans to address resistance. Strong leadership by WHO has been especially heartening. The World Health Assembly has recently endorsed a resolution on antimicrobial resistance directing WHO to lead the development of a Global Action Plan. PCAST believes the WHO Global Action Plan will play an important role in identifying global priorities and focusing national actions in the many areas needed to combat resistance, including stewardship, surveillance, and drug and diagnostics development.

The February 2014 launch of the Global Health Security Agenda (GHSa) by the United States in partnership with nearly 30 countries and WHO, OIE, and FAO, will provide an important platform to elevate antibiotic resistance as a global priority. The GHSa aims to accelerate progress toward a world safe and secure from infectious disease threats through nine major objectives, one of which focuses on “preventing the emergence and spread of drug-resistant organisms.” While the WHO Global Action Plan for antimicrobial resistance will guide international activities to combat resistance, the GHSa will provide important opportunities to secure financial resources and commitments to address antibiotic resistance.

The United States has taken a number of additional steps, which PCAST applauds, to promote international coordination on antibiotic resistance issues. At the United States–European Union

Summit in 2009, President Obama and then-European Council President Fredrik Reinfeldt established the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) to deepen technical cooperation between the United States and the European Union on combating resistance. TATFAR has made progress in a number of areas (summarized in the recent 2014 Progress Report),⁹⁸ and serves as a unique model for regional cooperation that could be emulated in other parts of the world.

Recommendation 8. Ensure Effective International Coordination

The Federal Government should vigorously support development of the WHO Global Action Plan and continue to elevate the issue of antibiotic resistance to the level of a global priority by encouraging or requiring, as appropriate, coordination among countries for surveillance, reporting, research, antibiotic stewardship, and development of new and next-generation drugs and diagnostics.

⁹⁸ Transatlantic Taskforce on Antimicrobial Resistance. *Transatlantic Taskforce on Antimicrobial Resistance: Progress Report*, May 2014. http://www.cdc.gov/drugresistance/pdf/TATFAR-Progress_report_2014.pdf.



Appendix A: Experts Consulted

PCAST is grateful for the input of the following individual experts. Listing here does not imply endorsement of this report or its recommendations.

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Appendix C: Current antibiotic-resistant threats in the United States

Microbe	Description	Threat Level	U.S. Infections /Year	U.S. Deaths/Year
<i>Clostridium difficile</i>	<i>Clostridium difficile</i> causes life-threatening diarrhea, most frequently in people who have had both recent medical care and antibiotics.	Urgent	250,000	14,000
Carbapenem-resistant Enterobacteriaceae (CRE)	CRE are a family of bacteria (that includes pathogens such as <i>Salmonella</i> and <i>E.coli</i> .) resistant to the carbapenem ⁹⁹ family of antibiotics. CRE have become resistant to all or nearly all the antibiotics currently available.	Urgent	9,300	610
Drug-resistant <i>Neisseria gonorrhoeae</i>	Multidrug- or cephalosporin-resistant gonorrhea is a sexually transmitted infection that can cause permanent reproductive health problems.	Urgent	246,000	<5
Multidrug-resistant <i>Acinetobacter</i>	<i>Acinetobacter</i> is a cause of pneumonia or bloodstream infections among critically ill patients.	Serious	7,300	500
Drug-resistant <i>Campylobacter</i>	<i>Campylobacter</i> causes diarrhea, fever, and abdominal cramps, and sometimes causes serious complications such as temporary paralysis.	Serious	310,000	28
Fluconazole-resistant <i>Candida</i>	<i>Candida</i> is a fungal infection and the fourth most common cause of health care-associated bloodstream infections in the United States.	Serious	3,400	220
Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)	Extended-spectrum β -lactamase is an enzyme that allows bacteria to become resistant to a wide variety of penicillins and cephalosporins, including extended spectrum cephalosporins.	Serious	26,000	1,700

⁹⁹ Carbapenems are considered drugs of 'last resort'

Vancomycin-resistant <i>Enterococcus</i> (VRE)	<i>Enterococci</i> cause a range of illnesses, including bloodstream infections, surgical site infections, and urinary tract infections.	Serious	20,000	1,300
Multidrug-resistant <i>Pseudomonas aeruginosa</i>	<i>Pseudomonas aeruginosa</i> is a common cause of health care-associated infections including pneumonia, bloodstream infections, urinary tract infections, and surgical site infections.	Serious	6,700	444
Drug-resistant non-typhoidal <i>Salmonella</i>	Non-typhoidal <i>Salmonella</i> usually causes diarrhea, fever, and abdominal cramps. Some infections spread to the blood and can have life-threatening complications.	Serious	100,000	38
Drug-resistant <i>Salmonella</i> Typhi	<i>Salmonella</i> serotype Typhi causes typhoid fever. Typhoid fever can lead to bowel perforation, shock, and death.	Serious	3,800 ¹⁰⁰	<5
Drug-resistant <i>Shigella</i>	<i>Shigella</i> usually causes diarrhea, fever, and abdominal pain. Sometimes it causes serious complications such as reactive arthritis.	Serious	27,000	40
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	MRSA causes a range of illnesses, from skin and wound infections to pneumonia and bloodstream infections that can cause sepsis and death. MRSA is one of the most common causes of health care-associated infections.	Serious	80,461	11,285
Drug-resistant <i>Staphylococcus pneumoniae</i>	<i>Streptococcus pneumoniae</i> is the leading cause of bacterial pneumonia and meningitis in the United States. It also is a major cause of bloodstream infections and ear and sinus infections.	Serious	1,200,000	7,000
Drug-resistant tuberculosis	Tuberculosis is among the most common infectious diseases and a frequent cause of death worldwide. Tuberculosis typically attacks the lungs, but can also affect other parts of the body.	Serious	1,042	50

¹⁰⁰ 21,700,000 infections worldwide

Vancomycin-resistant <i>Staphylococcus aureus</i> (VISA)	<i>Staphylococcus aureus</i> is a common type of bacteria that is found on the skin. When <i>Staphylococcus aureus</i> becomes resistant to vancomycin, there are few treatment options available.	Concerning	<5	<5
Erythromycin-resistant Group A <i>Streptococcus</i>	Group A <i>Streptococcus</i> causes many illnesses, including pharyngitis (strep throat), streptococcal toxic shock syndrome, necrotizing fasciitis ('flesh-eating' disease), scarlet fever, rheumatic fever, and skin infections such as impetigo.	Concerning	1,300	160
Clindamycin-resistant Group B <i>Streptococcus</i>	Group B <i>Streptococcus</i> is a type of bacteria that can cause severe illnesses in people of all ages, ranging from bloodstream infections (sepsis) and pneumonia to meningitis and skin infections.	Concerning	7,600	440



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