



U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON ENERGY AND COMMERCE

June 10, 2016

TO: Members, Subcommittee on Oversight and Investigations

FROM: Committee Majority Staff

RE: Hearing entitled “Combatting Superbugs: U.S. Public Health Responses to Antibiotic Resistance”

The Subcommittee on Oversight and Investigations will hold a hearing on Tuesday, June 14, 2016, at 10:00 a.m. in 2322 Rayburn House Office Building, entitled “Combatting Superbugs: U.S. Public Health Responses to Antibiotic Resistance.” The Subcommittee will hear testimony from U.S. public health officials on the current risks associated with “superbugs” resistant to antibiotics and the Federal government’s plans to confront this public health challenge.

I. WITNESSES

- Dr. Beth Bell, Director, National Center for Emerging and Zoonotic Infectious Disease, Centers for Disease Control;
- Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research, Food and Drug Administration;
- Dr. Richard Hatchett, Acting Director, Biomedical Advanced Research and Development Authority; and
- Dr. Dennis Dixon, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

II. BACKGROUND

a. Understanding the Superbug and Antibiotic Resistance

One of the world’s most pressing health problems is the emergence of bacterial infections that are resistant to antibiotics.¹ Since the discovery of penicillin in the early 20th century, almost every type of bacteria is becoming resistant to the antibiotic treatment designed to treat it. The

¹ The World Health Organization, *Antibiotic Resistance Fact Sheet*, October 2015, available at <http://www.who.int/mediacentre/factsheets/antibiotic-resistance/en/>.

continuing evolution of bacteria, the over-prescription of antibiotics, and the lack of new antibiotic development have contributed to this problem.

According to the Centers for Disease Control and Prevention (CDC), at least 2 million Americans fall sick every year with antibiotic-resistant infections, and 23,000 die.² Globally, some institutions estimate up to 700,000 die each year from antibiotic resistant infections.³ CDC Director Thomas Frieden has commented that “[t]he medicine cabinet is empty for some patients It is the end of the road unless we act urgently.”⁴ Without action, the researchers estimate 10 million people will die per year by 2050 from drug resistant infections.⁵

Medical professionals commonly define a “superbug” as a bacterial infection that is resistant to most or all antibiotics. Outbreaks of antibiotic-resistant bacteria occur most often in hospital settings, among patients receiving care for serious conditions. One of the most recent and high profile outbreaks occurred at the National Institutes of Health (NIH) Clinical Center. In 2012, the NIH announced that a type of Carbapenem-Resistant Enterobacteriaceae (CRE) had struck its clinical center, infecting 19 patients and killing seven.⁶ Over 70 bacteria are classified as CRE, including E.coli, and they typically exist in the digestive system. Over time, these bacteria have become resistant to last-resort antibiotics.

Dr. Frieden has described CRE as a “triple threat” because (1) the bacteria are resistant to all or nearly all antibiotics, (2) the bacteria kills up to half of patients who get bloodstream infections and (3) the bacteria can transfer their antibiotic resistance to other bacteria within the family, potentially making other bacteria untreatable.⁷ For example, according to Dr. Frieden, CRE can “spread the genes that destroy our last antibiotics to other bacteria, such as E. coli, and make E. coli resistant to antibiotics also.”⁸ This is significant because E. coli is the most common cause of urinary tract infections in healthy people.⁹ According to data reported to the CDC, the percentage of CRE resistant to antibiotics increased from 1.2 percent in 2001 to 4.2 percent in 2011.¹⁰

The issue of antibiotic resistance is again in the news because of a recent discovery of new antibiotic-resistant gene in Pennsylvania. Last month, a woman in Pennsylvania was diagnosed with an E. coli infection that had a rare gene called MCR-1, which makes it resistant

² Centers for Disease Control and Prevention, *Antibiotic/Antimicrobial Resistance*, available at: <https://www.cdc.gov/drugresistance/> (last visited June 8, 2016).

³ Review on Antimicrobial Resistance, *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations*, December 2014.

⁴ Jen Christensen and Debra Goldschmidt, *A Dreaded Superbug Found for the First Time in a U.S. Woman*, CNN, May 27, 2016.

⁵ Review on Antimicrobial Resistance, *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations*, December 2014.

⁶ Brian Vastag and Lena H. Sun, *NIH Superbug Claims 7th Victim*, THE WASHINGTON POST, Sept. 14, 2012.

⁷ Lena H. Sun, *CDC Says ‘Nightmare Bacteria’ a Growing Threat*, THE WASHINGTON POST, March 5, 2013.

⁸ *Id.*

⁹ *Id.*

¹⁰ Centers for Disease Control and Prevention, *Morbidity and Mortality Weekly Report, Vital Signs: Carbapenem-Resistant Enterobacteriaceae*, March 8, 2013.

to colistin, an antibiotic of last resort.¹¹ This antibiotic is used to treat patients with multiple drug-resistant infections, including CRE. However, colistin has very strong side effects and can cause kidney damage, so it is used in human patients only when absolutely necessary.¹²

The MCR-1 gene exists on a “plasmid,” which is a small piece of DNA that can move from one bacteria to another, spreading antibiotic resistance.¹³ In November 2015, Chinese and British researchers discovered the colistin-resistant strain in pigs, raw pork, and in a small number of people in China. The case of the woman in Pennsylvania is the first discovery of the rare MCR-1 gene in the United States. How the woman contracted the rare gene is unknown, but the CDC is currently investigating in coordination with the Department of Defense (DOD). The woman did not have CRE, and was eventually treated with other antibiotics and was released from medical supervision.

This discovery is troubling to health officials because it signals the potential arrival of an unstoppable superbug. The MCR-1 gene can join with a more common superbug, such as CRE, to create a bacterial infection that cannot be stopped with any known antibiotic treatment, which is known as a pan-resistant infection. In response to the discovery of the MCR-1 gene in the Pennsylvania case, Dr. Frieden commented that “[i]t basically shows us that the end of the road isn’t very far away for antibiotics—that we may be in a situation where we have patients in our intensive care units, or patients getting urinary-tract infections for which we do not have antibiotics.”¹⁴ At present, however, there is no evidence that the MCR-1 gene has merged with CRE to form a pan-resistant infection.

b. Overuse of Antibiotics

The over-use of antibiotics when they are not completely necessary is a major contributor to the growing problem of antibiotic-resistance. As soon as an antibiotic goes in to wide use among the general public, bacteria will evolve to become resistant. This happened with penicillin in the 1940s, when it became commonly prescribed to treat the general public.¹⁵

A study published last month in the *Journal of the American Medical Association* (JAMA) quantifies the overuse of antibiotics in the United States. The study found that nearly a third of antibiotics prescribed in doctors’ offices, emergency rooms, and hospital-based clinics in the United States are not needed.¹⁶ This amounts to nearly 47 million unnecessary prescriptions given out each year.¹⁷ Most of the unnecessary antibiotics are prescribed to treat respiratory

¹¹ Lena H. Sun and Brady Dennis, *The Superbug That Doctors Have Been Dreading Just Reached the U.S.*, THE WASHINGTON POST, May 27, 2016.

¹² Colistin is not used at all in farm animals in the U.S.

¹³ The Centers for Disease Control and Prevention, *Discovery of First MCR-1 gene in E. coli Bacteria Found in a Human in United States*, Media Statement, May 31, 2016.

¹⁴ Lena H. Sun and Brady Dennis, *The Superbug That Doctors Have Been Dreading Just Reached the U.S.*, THE WASHINGTON POST, May 27, 2016.

¹⁵ Julian Davies and Dorothy Davis, *Origins and Evolution of Antibiotic Resistance*, *Microbiol Mol Biol Rev*, Sept. 2010.

¹⁶ *Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011*, THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, May 3, 2016.

¹⁷ *Id.*

conditions such as the common cold, bronchitis, and other viral illnesses. Antibiotics are not effective against viral illnesses, but doctors sometime prescribe antibiotics anyway when they cannot determine whether the infection is bacterial or viral.

The CDC and the Pew Charitable Trust collaborated on this study, which analyzed CDC data for all antibiotic use in 2010 and 2011 in doctors' offices, emergency rooms, and hospital-based clinics.¹⁸ The numbers in the report most likely undercount the use of antibiotics, because the data did not include urgent care clinics, retail pharmacies, dentists' offices, and prescriptions given over the phone, and by nurse practitioners and physician assistants.¹⁹ About 13 percent of all outpatient visits in the United States result in an antibiotic prescription, which amounts to about 154 million visits annually.²⁰

Dr. Frieden has commented that over-use of antibiotics will lead to undesirable consequences:

Antibiotics are life-saving drugs, and if we continue down the road of inappropriate use we'll lose the most powerful tool we have to fight life-threatening infections Losing these antibiotics would undermine our ability to treat patients with deadly infections [and] cancer, provide organ transplants and save victims of burns and trauma.²¹

Although antibiotic overuse is commonplace in the United States, it is even more egregious across the globe. The World Health Organization has declared that humanity is on the precipice of a "post-antibiotic era," where common infections may once again be lethal because bacteria have become resistant to the antibiotics existing to treat them.²² The use of colistin, the antibiotic of last resort, is more common in Europe and Asia, and several recent studies from multiple countries show the emergence of colistin-resistant bacteria throughout the world.²³

c. Development of New Antibiotics

Although reducing the inappropriate and unnecessary use of antibiotics will slow the ability of bacteria to become resistant to known antibiotics, it alone will not solve the problem. New antibiotics must be developed. However, there are well-documented barriers to the discovery and development of new antibiotics.

¹⁸ *Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011*, THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, May 3, 2016.

¹⁹ Pranita D. Tamma and Sara E. Cosgrove, *Addressing the Appropriateness of Outpatient Antibiotic Prescribing in the United States: An Important First Step*, THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, May 3, 2016.

²⁰ *Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011*, THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, May 3, 2016.

²¹ The Centers for Disease Control and Prevention, *CDC: 1 in 3 Antibiotic Prescriptions Unnecessary*, Press Release, May 3, 2016.

²² World Health Organization, *Antimicrobial Resistance: Global Report on Surveillance*, 2014.

²³ The Pew Charitable Trusts, *A Scientific Roadmap for Antibiotic Discovery*, May 2016.

The last 30 years have marked a significant reduction in the discovery of new antibiotics. Currently, every antibiotic is a derivative of a type of antibiotic discovered from 1900 to 1984.²⁴ After the rush of discoveries of new antibiotics in the 1950s, discovery of new compounds as a foundation for antibiotics became more challenging for scientists, and new antibiotics became rarer over time. FDA approvals for antibiotics fell from 29 during the 1980s to just nine from 2000 to 2010.²⁵

In addition to the poor discovery prospects and gaps in scientific research, antibiotics are expensive to develop and offer a poor return on investment.²⁶ Antibiotic prescriptions are supposed to be limited to reduce bacterial resistance, and a new antibiotic on the market would be guarded closely. Doctors may be reticent to prescribe a new antibiotic that fights antibiotic-resistant infections, except in rare circumstances, because bacteria will become resistant to that antibiotic as soon as it becomes commonly used. Moreover, antibiotics are generally low-cost drugs designed to treat acute illnesses, so it is difficult for companies to make a profit.

An analysis by the Pew Charitable Trusts tracks new antibiotics in development, and found the current crop is insufficient to meet current or anticipated patient needs. In addition, few of the antibiotics in development can address the most antibiotic-resistant infections. As of March 2016, there were 37 new antibiotics in development. Of the 37 antibiotics in development, 11 were in phase 1 clinical trials, 13 in phase 2, and 13 in phase 3.²⁷ Historically, about 60 percent of drugs that enter phase 3 will be approved.²⁸ These drugs would potentially address many, but not all, resistant bacteria.

Of the approximately 34 companies with antibiotics in clinical development, only five are in the top 50 pharmaceutical companies by sales data.²⁹ About half of those companies are small companies that have no products on the market.³⁰

d. The Federal Response to Antibiotic Resistance

Public health officials have long warned about the risks of antibiotic resistance, and Congress and executive agencies have responded to these risks. Led by the Department of Health and Human Services (HHS), numerous Federal agencies have joined the effort to reduce the threat of antibiotic resistant bacteria. The CDC, the Food and Drug Administration (FDA), the NIH, and the Biomedical Advanced Research and Development Authority (BARDA) have all

²⁴ *Id.*

²⁵ The Pew Charitable Trusts, Infectious Diseases Society of America, Pharmaceutical Research and Manufacturers of America, *Reviving the Pipeline of Life-Saving Antibiotics: Exploring Solutions to Spur Innovation*, Conference proceedings, Sept. 22, 2011.

²⁶ The Pew Charitable Trusts, *A Scientific Roadmap for Antibiotic Discovery*, May 2016.

²⁷ The Pew Charitable Trusts, *Tracking the Pipeline of Antibiotics in Development*, March 2014, updated May 2016, available at <http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2014/03/12/tracking-the-pipeline-of-antibiotics-in-development>.

²⁸ Michael Hay et al., *Clinical Development Success Rates for Investigational Drugs*, *Nature Biotechnology* 32 (2014).

²⁹ The Pew Charitable Trusts, *Tracking the Pipeline of Antibiotics in Development*, March 2014, updated May 2016, available at <http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2014/03/12/tracking-the-pipeline-of-antibiotics-in-development>

³⁰ *Id.*

made significant and ongoing contributions to thwart the spread of antibiotic resistant bacterial infections.

Congress has acted to encourage the innovation and discovery of new antibiotics. As part of the Food and Drug Administration Safety and Innovation Act, the Generating Antibiotic Incentives Now (GAIN) Act was signed into law in 2012. The purpose of the GAIN Act was to promote the development and expedite the FDA approval process of antibiotics to treat life-threatening infections. To promote antibiotic development, the GAIN Act added an additional 5 years of exclusivity, which means that a generic form of the antibiotics may not be produced for an additional 5 years. This allows drug companies extra time to recoup production costs and increases the incentive for drug companies to research and develop new antibiotics. The Antibiotic Development to Advance Patient Treatment (ADAPT) Act builds on this progress, and passed through the House as part of the 21st Century Cures legislation last year. The ADAPT legislation aims to encourage development of antibiotics for life threatening bacterial infections and provides an alternative regulatory pathway for limited-population antibiotics.

In March 2015, the White House released a National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) in response to an Executive Order issued by President Obama in September 2014.³¹ This action plan outlines steps to implement a national strategy to combat antibiotic resistance and addresses policy recommendations made by the President's Council of Advisors on Science and Technology.

The National Action Plan listed five goals:

- Slow the emergence of resistance bacteria and prevent the spread of resistant infections;
- Strengthen national one-health surveillance efforts to combat resistance;
- Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria;
- Accelerate basic and applied research and development for new antibiotics, other therapeutics and vaccines; and
- Improve international collaboration and capacities for antibiotic-resistance prevention, surveillance, control and antibiotic research and development.

The plan also created a Task Force comprised of representatives from the Federal agencies charged with implementing the plan.³² Congress has increased funding for these initiatives by 57 percent over last fiscal year, for a total of more than \$375 million.³³

³¹ The White House, *National Action Plan for Combating Antibiotic-Resistant Bacteria*, March 2015.

³² *Id.*

³³ For the 2016 fiscal year, Congress allocated \$160 million to the Centers for Disease Control and Prevention, \$100 million to the National Institutes of Health, and \$96 million to BARDA.

The action plan states that by 2020, implementation of the plan will lead to major reductions in the “incidence of urgent and serious threats” from antibiotic-resistant bacteria, “improved antibiotic stewardship in healthcare settings,” “expanded surveillance for drug-resistant bacteria in humans and animals,” and the “development of two or more antibiotic drug candidates or non-traditional therapeutics for treatment of human disease.”³⁴

In November 2015, the Task Force released its “First 180 Days Report” monitoring the progress of the action plan. The report highlighted notable achievements, including new antibiotic stewardship guidelines for nursing homes from the CDC.³⁵ In March 2016, the President’s Advisory Council on Combating Antibiotic-Resistant Bacteria issued “initial assessments” of the progress on the action plan.³⁶

Two of the Council’s six recommendations addressed the need for Federal coordination across agencies. The Council noted that “centrally coordinated mechanisms were not sufficient to ensure maximum synergy, avoidance of duplication, and coverage of all key points.”³⁷ The Council also recommended selecting a “champion in the [U.S. Government] to align all of the agencies and move the work forward efficiently and synergistically.”³⁸ These recommendations were made to the HHS Secretary, to advise and support the implementation of the CARB Action Plan.

Mapping the Spread of Antibiotic-Resistant Bacteria

The CDC has led the coordinated effort between the DOD and the U.S. Department of Agriculture (USDA) to respond to the most recent discovery of MCR-1 in Pennsylvania. The CDC is currently identifying and investigating the Pennsylvania woman’s close contacts to try to identify whether any of them was the source of the MCR-1 gene. According to a briefing by the CDC provided to committee staff, unconfirmed testing of samples from the 20 high-risk contacts so far do not show the MCR-1 gene. The USDA has also been investigating the source of the MCR-1 gene, and discovered the gene in a pig in the United States. The USDA is currently working to identify the source of that gene as well.³⁹

These efforts are made possible by the National Antimicrobial Resistance Monitoring System program, which monitors antimicrobial resistance across bacteria discovered in food, animals, humans, and meats. The FDA, CDC, and USDA all conduct research on bacteria found through these surveillance methods, to determine how the resistance arises and transfers between bacteria.⁴⁰

³⁴ The White House, *National Action Plan for Combating Antibiotic-Resistant Bacteria*, March 2015.

³⁵ Taskforce for Combating Antibiotic Resistant Bacteria, *First 180 Days Report*, November 2015.

³⁶ Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, *Initial Assessments of the National Action Plan for Combating Antibiotic-Resistant Bacteria*, March 2016.

³⁷ *Id.*

³⁸ *Id.*

³⁹ The Department of Health and Human Services, *Blog Post: Proactive Efforts by U.S. Federal Agencies Enable Early Detection of New Antibiotic Resistance*, May 26, 2016.

⁴⁰ The Food and Drug Administration, National Antimicrobial Resistance Monitoring System, *available at* <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/> (last visited June 8, 2016).

As part of the CARB Action Plan, CDC is ramping up its network of regional and local labs to track the spread of the MCR-1 gene and other new forms of antibiotic resistance. Set to begin in fall of 2016, the “Antibiotic Resistance Lab Network” will provide the capacity for seven to eight regional labs charged with detecting and responding to bacteria-resistant organisms, and reporting these instances to the CDC.⁴¹

Antibiotic Stewardship Programs

In addition to assembling new data to track the use of antibiotics and the spread of these resistant bacteria, CDC has partnered with FDA to advocate for antibiotic “stewardship” programs in health care facilities throughout the United States.⁴² The CDC has issued guidelines about how hospitals can minimize inappropriate or excessive use of antibiotics, which could reduce antibiotic over-prescription.⁴³ Not all health care facilities have implemented stewardship programs, but the Centers for Medicare and Medicaid Services is expected to release a proposed rule that would require hospitals to have antibiotic stewardship programs in place before they can receive reimbursements from Medicare and Medicaid.⁴⁴

New Antibiotic Development

Scientists and medical professionals have noted that the current crop of candidate antibiotics in development is insufficient to counter the current threat of antibiotic resistant bacteria. In May 2015, there were 28 antibiotics in Phase II/Phase III clinical development, compared to over 500 candidates in Phase II/Phase III clinical development for oncology indications.⁴⁵ BARDA is responsible for developing and procuring medical countermeasures to address public health threats, including bacterial infections caused by antibiotic resistant bacteria.

In February 2016, BARDA collaborated with the National Institutes of Allergy and Infectious Diseases (NIAID) to establish a “Biopharmaceutical Accelerator” that will “support research and development to accelerate candidate products (drugs, vaccines, and diagnostics) into clinical development.”⁴⁶ This program furthers the goals set out in the Administration’s CARB Action Plan to incentivize antibacterial drug development. According to BARDA, the Accelerator will (1) fund development of antibacterial products, (2) quickly move successful

⁴¹ Centers for Disease Control and Prevention, *Antibiotic Resistance Solutions Initiative*, available at <http://www.cdc.gov/drugresistance/solutions-initiative/> (last visited June 8, 2016).

⁴² U.S. Food and Drug Administration, *Get Smart: Know When Antibiotics Work Campaign*, available at <http://www.cdc.gov/getsmart/community/materials-references/index.html> (last visited June 8, 2016)

⁴³ The Centers for Disease Control and Prevention, *Core Elements of Hospital Antibiotic Stewardship Programs*, 2014.

⁴⁴ Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, *Initial Assessments of the National Action Plan for Combating Antibiotic-Resistant Bacteria*, March 2016.

⁴⁵ Office of the Assistant Secretary for Preparedness and Response, *BARDA Seeks to Launch a Novel Partnership, A Product Accelerator to Address Antimicrobial Resistance*, Feb. 19, 2016, available at <http://www.phe.gov/ASPRBlog/pages/BlogArticlePage.aspx?PostID=176>.

⁴⁶ *Id.*

drug candidates through early development, (3) provide business and drug development guidance, and (4) decrease barriers to research and development of antibiotics.⁴⁷

The NIAID has been funding and conducting research on antimicrobial resistance, including basic research on how bacteria develop resistance, diagnostics, and clinical trials to find vaccines and treatments that are effective against antibiotic-resistant bacteria.⁴⁸ NIH has also funded studies to evaluate alternative therapies to traditional antibiotics.

III. ISSUES

The following issues will be examined at the hearing:

- The status of the current threats of antibiotic-resistant bacteria in the United States and around the world;
- The coordination among agencies on activities to combat antibiotic-resistant bacteria;
- The development of new antibiotics and alternative therapies to treat bacteria that are resistant to all or nearly all antibiotics; and
- The role of the Congress, and the Energy and Commerce Committee in particular, in shaping the response to antibiotic-resistant bacteria.

IV. STAFF CONTACTS

If you have any questions regarding the hearing, please contact Alan Slobodin, Emily Felder, or Brittany Havens at (202) 225-2927.

⁴⁷ *Id.*

⁴⁸ National Institute of Allergy and Infectious Diseases, *Antimicrobial Resistance*, March 14, 2016, available at <https://www.niaid.nih.gov/topics/antimicrobialresistance/Pages/default.aspx>.