COMBATING SUPERBUGS: U.S. PUBLIC HEALTH RESPONSES TO ANTIBIOTIC RESISTANCE

HEARING
BEFORE THE
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
OF THE
COMMITTEE ON ENERGY AND COMMERCE
HOUSE OF REPRESENTATIVES
ONE HUNDRETH FOURTEENTH CONGRESS
SECOND SESSION
JUNE 14, 2016
Serial No. 114–153

Printed for the use of the Committee on Energy and Commerce
energycommerce.house.gov
U.S. GOVERNMENT PUBLISHING OFFICE
WASHINGTON : 2017
CONTENTS

Hon. Tim Murphy, a Representative in Congress from the Commonwealth of Pennsylvania, opening statement .................................................. 1
Prepared statement ................................................................................................................................. 3
Hon. Diana DeGette, a Representative in Congress from the state of Colorado, opening statement ............................................................................................................. 4
Hon. Fred Upton, a Representative in Congress from the State of Michigan, opening statement ................................................................. 6
Prepared statement ................................................................................................................................. 7
Hon. David B. McKinley, a Representative in Congress from the State of West Virginia, opening statement ......................................................... 8
Prepared statement ................................................................................................................................. 8
Hon. Frank Pallone, Jr., a Representative in Congress from the State of New Jersey, opening statement ............................................................................................................. 9

WITNESSES

Beth Bell, Director, National Center for Emerging and Zoonotic Infectious Disease, Centers for Disease Control ................................................................. 12
Prepared statement ................................................................................................................................. 14
Janet Woodcock, Director, Center for Drug Evaluation and Research, Food and Drug Administration ............................................................................................................. 21
Prepared statement ................................................................................................................................. 23
Richard J. Hatchett, Acting Director, Biomedical Advanced Research And Development Authority ............................................................................................................. 34
Prepared statement ................................................................................................................................. 36
Dennis M. Dixon, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health ... 45
Prepared statement ................................................................................................................................. 47

SUBMITTED MATERIAL

Committee memorandum ........................................................................................................................... 79
COMBATING SUPERBUGS: U.S. PUBLIC HEALTH RESPONSES TO ANTIBIOTIC RESISTANCE

TUESDAY, JUNE 14, 2016

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:00 a.m., in room 2322, Rayburn House Office Building, Hon. Tim Murphy (chairman of the subcommittee) presiding.

Present: Representatives Murphy, McKinley, Burgess, Blackburn, Bucshon, Flores, Brooks, Mullin, Hudson, Collins, Upton (ex officio), DeGette, Schakowsky, Castor, Tonko, Clarke, Kennedy, Green, and Pallone (ex officio).

Staff Present: Gary Andres, Staff Director; Emily Felder, Counsel, Oversight and Investigations; Jay Gulshen, Staff Assistant; Brittany Havens, Oversight Associate, Oversight and Investigations; Charles Ingebritson, Chief Counsel, Oversight and Investigations; Alan Slobodin, Deputy Chief Counsel, Oversight; Dylan Vorbach, Deputy Press Secretary; Jeff Carroll, Minority Staff Director; Tiffany Guarascio, Minority Deputy Staff Director and Chief Health Advisor; Chris Knauer, Minority Oversight Staff Director; Una Lee, Minority Chief Oversight Counsel; Elizabeth Letter, Minority Professional Staff Member; and Andrew Souvall, Minority Director of Communications, Outreach and Member Services.

OPENING STATEMENT OF HON. TIM MURPHY, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. MURPHY. Good morning, meeting here of the Energy and Commerce Subcommittee on Oversight and Investigations. I do want to announce to members this hearing is here and not in Room 2123. I just want you to know. I was there, you were not. It was a very powerful, moving——

Mr. UPTON. There was a very long line of folks to get in.

Mr. MURPHY. There was, so I figured it must be this hearing, but my apologies. It happens.

So this is a hearing on U.S. public health response to antibiotic resistance. The subcommittee convenes this hearing today to examine public health responses to the challenge of antibiotic-resistant superbugs. One of the world’s most pressing health problems is the emergence of bacterial infections that are resistant to antibiotics.
And according to the Centers for Disease Control and Prevention, each year, 2 million Americans become sick with antibiotic-resistant infections, and of that, about 23,000 die. Globally, some institutions estimate up to 700,000 die each year from antibiotic-resistant infections, and without action, the researchers estimate 10 million people will die per year by 2050 from drug-resistant infections.

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.

The antibiotic-resistance threat just got greater. Last month, a woman in my home State of Pennsylvania was diagnosed with an E. coli infection that had a rare gene called MCR–1, a new kind of superbug never before seen in the United States. Medical professionals were alarmed for two reasons. One, this new superbug is resistant to colistin, an antibiotic of last resort, which is used when no other antibiotics can fight the infection. And two, this MCR–1 gene can move from one bacteria to another. Eventually, MCR–1 could emerge with another superbug that is resistant to all antibiotics except for colistin and form an unstoppable superbug.

In response to the discovery of the MCR–1 gene, CDC Director Dr. Tom Frieden commented that the medicine cabinet is empty for some patients. It is the end of the road unless we act urgently. If this threat is not stopped, minor infections may become life-threatening and treatment for diseases such as cancer, diabetes, or routine surgeries will be at risk.

Fortunately, the end of the road is not here yet, and Congress and Federal agencies are working diligently to counter the effects of antibiotic resistance. These efforts confront the two main contributors to the spread of antibiotic resistance: the overprescription of antibiotics and the lack of new antibiotic development.

Since the discovery of penicillin in the early 20th century, almost every type of bacteria has become less responsive to antibiotics. As soon as an antibiotic goes into wide use among the general public, bacteria evolve to become resistant.

A study published last month in the Journal of the American Medical Association, known as JAMA, found that nearly a third of antibiotics prescribed in doctors' offices, emergency rooms and hospital-based clinics in the United States are not needed. This amounts to nearly 47 million unnecessary prescriptions given out each year. That is 47 million unnecessary prescriptions each year. And the number in this report most likely undercount the use of antibiotics because the data did not include urgent care clinics, retail pharmacies, dentist offices, and prescriptions given over the phone by nurse practitioners and physician assistants.

To combat antibiotic overuse, the CDC has partnered with the FDA to advocate for antibiotic stewardship programs in health care facilities throughout the United States. The CDC has issued guidelines about how hospitals can minimize inappropriate or excessive use of antibiotics, which could help reduce antibiotic overprescription. Reducing the inappropriate use of antibiotics will help, but it can only slow the spread of antibiotic-resistant bacteria, new antibiotics, and alternative therapies must be developed.
Despite the need for antibiotic development, as of March 2016 there were only 37 new antibiotics in development, and just 13 were in phase 3 clinical trials. These drugs would potentially address many resistant bacteria, but they are not enough. To combat this, in February of this year the Biomedical Advanced Research and Development Authority, known as BARDA, has collaborated with NIH to establish a biopharmaceutical accelerator that will support research and development to incentivize antibacterial drug development. This accelerator will, one, fund development of antibacterial products; and two, quickly move successful drug candidates through early development; three, provide business and drug development guidance; and four, decrease barriers to research and development of antibiotics.

The CDC, FDA, NIH, and BARDA have and continue to make significant and ongoing contributions to implement the National Action Plan for Combating Antibiotic-Resistant Bacteria released last year, which outlines steps to implement a national strategy to combat antibiotic resistance. Additionally, Congress has increased funding for these initiatives by 57 percent over last fiscal year for a total of more than $375 million.

Despite these promising developments, we are facing a public health challenge, and we need to ensure that the Federal Government is taking the appropriate action to protect the American public.

So I want to thank the witnesses for appearing here today before the subcommittee. I look forward to hearing all of your testimony on this very, very important issue.

[The prepared statement of Mr. Murphy follows:]

**PREPARED STATEMENT OF HON. TIM MURPHY**

The subcommittee convenes this hearing today to examine public health responses to the challenge of antibiotic resistant "superbugs."

One of the world’s most pressing health problems is the emergence of bacterial infections that are resistant to antibiotics.

According to the Centers for Disease Control and Prevention, each year 2 million Americans become sick every year with antibiotic-resistant infections, and of that about 23,000 die.

Globally, some institutions estimate up to 700,000 die each year from antibiotic resistant infections. Without action, the researchers estimate 10 million people will die per year by 2050 from drug resistant infections.

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.

The antibiotic-resistance threat just got greater. Last month, a woman in my home state of Pennsylvania was diagnosed with an E. coli infection that had a rare gene called MCR–1, a new kind of superbug never before seen in the United States.

Medical professionals were alarmed for two reasons. One, this new superbug is resistant to colistin [Co—liss—tin], an antibiotic of last resort which is used when no other antibiotics can fight the infection.

Two, this MCR–1 gene can move from one bacteria to another. Eventually, MCR–1 could merge with another superbug that is resistant to all antibiotics, except for colistin, and form an unstoppable superbug.

In response to the discovery of the MCR–1 gene, CDC Director Dr. Tom Frieden commented that “the medicine cabinet is empty for some patients . . . . It is the end of the road unless we act urgently.” If the threat is not stopped, minor infections may become life threatening and treatment for disease such as cancer, diabetes or routine surgeries will be at risk.

Fortunately, the end of the road is not here yet. Congress and Federal agencies are working diligently to counter the effects of antibiotic resistance.
These efforts confront the two main contributors to the spread of antibiotic resistance: The over-prescription of antibiotics and the lack of new antibiotic development.

Since the discovery of penicillin in the early 20th century, almost every type of bacteria has become less responsive to antibiotics. As soon as an antibiotic goes into wide use among the general public, bacteria evolve to become resistant.

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

And the numbers in this 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.

To combat antibiotic over-use, the CDC has partnered with FDA to advocate for antibiotic “stewardship” programs in health care facilities throughout the United States. The CDC has issued guidelines about how hospitals can minimize inappropriate or excessive use of antibiotics, which could help reduce antibiotic over-prescription.

Reducing the inappropriate use of antibiotics will help, but it can only slow the spread of antibiotic resistant bacteria. New antibiotics and alternative therapies must be developed.

Despite the need for antibiotic development, as of March 2016, there were only 37 new antibiotics in development. Just 13 were in phase 3 clinical trials. These drugs would potentially address many resistant bacteria—but they are not enough.

To combat this, in February of this year, the Biomedical Advanced Research and Development Authority (BARDA) has collaborated with NIH to establish a “Biopharmaceutical Accelerator” that will support research and development to incentivize antibacterial drug development. This Accelerator will (1) fund development of antibacterial products, (2) quickly move successful drug candidates through early development, (3) provide business and drug development guidance, and (4) decrease barriers to research and development of antibiotics.

Mr. Murphy. I now recognize the Ranking Member of the subcommittee, Ms. DeGette of Colorado, for 5 minutes.

Ms. DeGette. Thank you so much, Mr. Chairman. This is a really important hearing. We have been worried for quite some time here in Congress and at the agencies about the risk of resistant antibiotics. And this report last month about the superbug has been quite concerning to all of us.

The bacterium’s resistance to colistin is particularly concerning because in this country physicians use colistin as the treatment of last resort when other antibiotics are no longer effective. Public health experts fear that this gene could jump to other bacteria that are already resistant to most other antibiotics.
Here is another observation about Dr. Frieden. He said, “It basically shows 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.”

Obviously, we are all concerned about this, and I know all the witnesses and the members share this concern. We really don’t want to revert to a time when physicians no longer have the tools to treat infections. Even common and once easily treated infections could once again prove life-threatening.

That this newest superbug has emerged on our home turf should not surprise us. Public health and infectious disease experts have been sounding the alarm for years. But I hope that this new discovery will lend urgency to efforts to monitor and fight antibiotic resistance.

The CDC has reported for decades that overuse of antibiotics and poor hygiene practices in hospitals and other inpatient health care settings contribute to the formation of drug-resistant bacteria. For example, studies showed that 30 to 50 percent of antibiotics prescribed in hospitals were unnecessary or inappropriate. Public health experts have similarly warned us about overprescribing of antibiotics in outpatient settings. A recent Pew study, for example, found that about 30 percent of all outpatient office visits in the U.S. resulted in the prescribing of an antibiotic, but 30 percent of those, which is almost 50, 5–0 million prescriptions are unnecessary.

Now, in the last decade these issues have received increased attention and funding, but as our witnesses will testify today, there is still far more to do. And I want to hear from our witnesses in particular in two different areas. The first one is antibiotic stewardship programs, which can both decrease the spread of infections and reduce the inappropriate use of antibiotics.

We need to improve public health education to ensure that patients and physicians understand how and when antibiotics should be prescribed. We need such stewardship programs both in health care facilities like hospitals and also in communities. I am hoping I can hear from our witnesses about antibiotic stewardship and whether we are seeing positive outcomes from current efforts.

I also am interested to see how antibiotic stewardship programs can result in more appropriate and effective use of antibiotics in animals. I think more needs to be done to shed a light on these issues, and I am interested to see what the witnesses will have to say. I do wish that we had a witness from the USDA because antibiotic overuse in animals is a really big problem.

The second area I want to hear about is the development of new antibiotics, diagnostics, and even vaccines to address the issue of antibiotic resistance. All of these agencies today play a critical role in the development of new drugs and other tools.

I can’t lose the opportunity to talk about our wonderful bill that Chairman Upton and I have cosponsored, along with all the other members of this subcommittee. Earlier this year, the 21st Century Cures Act passed out of the Energy and Commerce Committee unanimously and was then passed by the full House on an overwhelming basis. The bill includes the text of the Antibiotic Devel-
development to Advance Patient Treatment Act, or ADAPT Act. This is a really important bill that was originally cosponsored by Congress- man Green and Congressman Shimkus, and it creates a new FDA approval pathway for limited population antibacterial drugs.

This legislation is designed to provide an approval process for drugs that affect a limited population of patients with serious or life-threatening infections or for drugs that fill an unmet need. We really need to pass the ADAPT Act. The easiest way to do this is of course for the Senate to pass the 21st Century Cures bill, and frankly, we keep hearing assurances that this will be happening any day. So maybe this urgent issue can be used to help enact this important law into law.

So, Mr. Chairman, I really want to thank you for having this hearing. It is an important one. And I want to thank our witnesses again for coming today, and I yield back.

Mr. MURPHY. The gentlelady yields back. I now recognize the chairman of the full committee, Mr. Upton, for 5 minutes.

OPENING STATEMENT OF HON. FRED UPTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. UPTON. Well, thank you, Mr. Chairman.

So today, we gather to discuss the U.S. public health response to antibiotic resistance in light of the recent discovery of a new superbug. This superbug gene was first discovered by Chinese and British researchers in pigs, raw pork, and in a small number of folks in China in November of last year, but a recent case of course of the woman in Pennsylvania with the E. coli is the first discovery of this rare gene known as MCR here in the U.S.

A headline in the Post captured the urgency: “The superbug that doctors have been dreading just reached the U.S.” Concerns about this new threat are real indeed and they are being felt in Michigan and throughout the country.

The detection of this new antibiotic-resistant gene is very troubling because it signals the potential arrival of an unstoppable superbug. The gene is resistant to a last-report antibiotic and has the ability to move from one bacterium to another. While MCR–1 on its own is treatable by other antibiotics, disease experts tell us that the fear is not if but when this gene transfers and merges with another superbug that is resistant to all other antibiotics. This would create the nightmare scenario of a bacterial infection that cannot be stopped with any known antibiotic treatment.

The continuing evolution of bacteria, the overprescription of antibiotics, and the lack of new antibiotic development have all contributed to the problem. Our understanding of the MCR–1 gene is growing by the day, but there are still many questions that remain to be answered before we can be assured that we are doing everything that we can to protect the American people from this superbug and future challenges that arise from antibiotic resistance.

The questions include how did the bug get here to the U.S.? Where did it come from? How does it spread? Are we prepared for an outbreak of antibiotic-resistant bacterium? What is the Federal Government’s plan to confront the public health challenge? In addition to our concerns about this particular superbug, we need to
take a look at antibiotic resistance as a whole. And in response to the
discovery of MCR gene in Pennsylvania, Dr. Frieden commented that it basically shows us that the end of the road isn’t
very far away for antibiotics. If that is true, minor bacterial infec-
tions could suddenly become fatal.

So we need to evaluate antibiotic development and assess where
the science is, what barriers exist. How do we promote the dis-
cover of new antibiotics? And as my good friend and colleague Ms.
DeGette said, through the GAIN Act of 2012 and the ADAPT Act,
which is part of 21st Century Cures, this committee has made a
good number of strides to foster and encourage the development of
new antibiotics that can fight the superbugs. In the meantime, we
need to take appropriate measures such as antibiotic stewardship
program to ensure that the antibiotics that already exist are being
prescribed appropriately.

[The prepared statement of Mr. Upton follows:]

PREPARED STATEMENT OF HON. FRED UPTON

Today, we gather to discuss the U.S. public health response to antibiotic resist-
ance in light of the recent discovery of a new superbug.

This superbug gene was first discovered by Chinese and British researchers in
pigs, raw pork, and in a small number of people in China in November last year,
but a recent case of a woman in Pennsylvania with E. coli is the first discovery of
this rare gene, known as MCR–1, in the United States. A headline in The Wash-
ington Post captured the urgency—"The superbug that doctors have been dreading
just reached the U.S." Concerns about this new threat are real, and they are being
felt in Michigan and throughout the country.

The detection of this new antibiotic-resistant gene is troubling because it signals
the potential arrival of an unstoppable superbug. This gene is resistant to a last-
resort antibiotic and has the ability to move from one bacterium to another. While
MCR–1 on its own is treatable by other antibiotics, disease experts tell us the fear
is not if, but when, this gene transfers and merges with another superbug that is
resistant to all other antibiotics. This would create the nightmare scenario of a bac-
terial infection that cannot be stopped with any known antibiotic treatment.

The continuing evolution of bacteria, the over-prescription of antibiotics, and the
lack of new antibiotic development have all contributed to this problem. Our under-
standing of the MCR–1 gene is growing by the day, but there are still many ques-
tions that remain to be answered before we can be assured that we are doing every-
thing that we can to protect the American people from this superbug and future
challenges that arise from antibiotic-resistance.

The questions include: How did the bug get to the United States? Where did it
come from? How does it spread? Are we prepared for an outbreak of an antibiotic-
resistant bacterium? What is the federal government’s plan to confront this public
health challenge?

In addition to our concerns about this particular superbug, we need to take a look
at antibiotic resistance as a whole. In response to the discovery of the MCR–1 gene
in the Pennsylvania case, the CDC Director, Dr. Tom Frieden, commented that "it
basically shows us that the end of the road isn’t very far away for antibiotics." If
that is true, minor bacterial infections could suddenly become fatal.

We need to evaluate antibiotic development and assess where the science is, what
barriers exist, and how we can promote the discovery of new antibiotics. Through
the GAIN Act in 2012, and the ADAPT Act which is part of 21st Century Cures,
this committee has made numerous strides to foster and encourage the development of
new antibiotics that can fight these superbugs.

In the meantime, we need to take appropriate measures, such as antibiotic stew-
ardship programs, to ensure that antibiotics that already exist are being prescribed
appropriately.

We thank the experts joining us this morning to discuss the federal response to
this superbug and how antibiotic resistance is being addressed both as a nation and
globally. The last thing we can afford is looking back to today, and wishing we had
done more.
Mr. UPTON. I appreciate the testimony and the dialogue with our experts, and I yield back to Mr. McKinley.

OPENING STATEMENT OF HON. DAVID B. MCKINLEY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF WEST VIRGINIA

Mr. MCKINLEY. Thank you, Mr. Chairman.

Antibiotics, it is my understanding—I am the engineer in the room, not the practicing physician, but my understanding is that the antibiotics are not effective against viruses, and this seems to be a good scientific fact from which to begin with. But yet in America you have heard the statistics. A third of the antibiotics are overprescribed by doctors. The CDC said that 47 million prescriptions were unnecessarily prescribed or inappropriately prescribed for cases that don't respond to the antibiotics.

And then the other point it comes down to is that we only represent 5 percent of the population in the world, so we have got 95 percent of the world out there—in many respects we know there are 20 nations in Europe and we know Mexico gives you antibiotics over the counter. And that tends to get to a point where we are probably going to overprescribe or they are going to be inappropriately used and our body will be able to build up resistance to that as a result of this inappropriate use for that.

And then we go to this, fast-forward to today with the woman in Pennsylvania. The interesting part is going to be how we are going to respond to that because how did she get it and what are we going to do to respond to that? So watching the time frame with this, we don't know if these antibiotics are used to help will even be effective in the future because of this overuse, overprescription.

[The prepared statement of Mr. McKinley follows:]

PREPARED STATEMENT OF HON. DAVID B. MCKINLEY

Thank you, Mr. Chairman, and thank you for holding this hearing on this important public health challenge.

When we think about superbugs, or antibiotic resistant bacteria, we think about two different categories: what we know, and what we don't know.

We know that doctors and patients alike are partially to blame for the over-use of antibiotics. Doctors prescribe antibiotics when they are not necessary, and patients ask for antibiotics, thinking they will make them better, faster.

We know that antibiotics are becoming less effective in treating bacterial infections, because bacteria are evolving to become resistant. This will make it harder to treat not only common infections, such as strep throat, but also more serious conditions like cancer.

Patients fighting cancer undergo treatment that damages the immune system, which makes them more susceptible to infections. The same is true for organ transplant patients.

We know that the current crop of antibiotics in development and clinical trials are not sufficient. Researchers are starting to examine alternative therapies, other than antibiotics, to treat bacterial infections.

Now, on to what we don't know. We don't know how the dangerous MCR–1 gene came into the United States. We don't know how the woman in Pennsylvania contracted the MCR–1 gene, since she had not traveled outside the United States recently, and tests did not find the gene in her close family and friends.

We don't know how long it will take for the MCR–1 gene to transfer to bacteria that are resistant to all other antibiotics to create bacteria that cannot be treated with existing antibiotics. And when that happens, we don't know how far or how quickly it will spread, and how doctors will treat it.

Fortunately, Congress and Federal agencies are taking action, and they did not wait until this MCR–1 gene showed up. Over the last several years, the Federal gov-
ernment has ramped up its efforts to surveil and track these dangerous bacteria so that scientists and medical professionals can be as prepared as possible to confront these threats.

The CDC has led the coordinated effort between the DOD and the USDA to respond to the discovery of 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.

Through the National Antimicrobial Resistance Monitoring System, the FDA, CDC, and USDA all conduct research on bacteria found in food, animals, and humans. These surveillance methods track the bacteria and determine how resistance arises and transfers between bacteria.

Also, as part of a National 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.

The more we know about these superbugs—where they are, how they become resistant, and how they are transmitted to humans—the more we can prepare as a nation to combat these challenges.

Thank you to our witnesses for testifying today, and I look forward to a productive conversation.

Mr. McKinley. So I am looking forward to your testimony today, and I yield back the balance of my time to Dr. Burgess.

Mr. Burgess. I thank the gentleman for yielding. And I do want to thank our panelists for being here today. And I am most interested in knowing how you all are going to be working together on an interagency basis to see that we achieve the goals. I would like to hear from you perhaps some of your thoughts on what the legislative branch might do in addition to getting the Cures bill passed over in the other body.

And then finally, there was a significant amount of money made available in this area last December, and I would like to hear from each of you how that money has been allocated and utilized and as to whether or not you thought it had been of any benefit.

Thank you, Mr. Chairman. I will yield back.

Mr. Murphy. Thank you. I now recognize the ranking member of the full committee, Mr. Pallone, for 5 minutes.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. Pallone. Thank you, Mr. Chairman.

Antibiotic resistance is a significant domestic and global threat to both public health and national security, and I am glad we are taking the opportunity to examine this issue. I want to begin by emphasizing that antibiotics are incredibly valuable tools that have made once-fatal infections easily treatable, and antibiotics have transformed our health care system.

But as the use of antibiotics has spread, the threat posed by antibiotic-resistant bacteria or superbugs has grown. For that effective, coordinated, and decisive government action, we risk entering into a post-antibiotic world where common infections could once again become life-threatening.

The recent discovery of the MCR–1 gene on a colistin-resistant strain of the E. coli bacteria signals that this day is closer than it has ever been before. We see alarming statistics about the rates of overprescribing of antibiotics both for unnecessary and inappropriate use. At the same time, we have seen that drug manufacturers are unable to produce enough new drugs to meet this threat.
There is no question that our arsenal of effective antibiotics is dangerously low today as a result of antibiotic resistance, and it is a dire situation.

That said, I am encouraged by the attention and funding we have placed on antibiotic resistance in recent years. Last year, the White House unveiled its National Action Plan for Combating Antibiotic-Resistant Bacteria, which sets forth ambitious goals to fight antibiotic resistance. All the agencies before us today play critical roles in that effort. In fiscal year 2016, we are devoting over $830 million to fighting antibiotic resistance, and President Obama has requested $1.1 billion towards this effort for fiscal year 2017. And these are important investments.

But in order for us to effectively address antibiotic resistance we need to make this a priority for the foreseeable future. This is not an issue we can address for a few years and then ignore. Antibiotic resistance is a reality of nature. Bacteria begin to mutate and develop resistance as soon as a new antibiotic begins to be used. We must develop long-term strategies and guarantee long-term funding to fight antibiotic resistance, and once we have begun implementing those strategies and ramping up funding, we must follow through on our commitments.

It is also important to emphasize that this is a global threat. It is not enough to address resistance here in the United States and hope that it will keep us protected. And from a global perspective, we must recognize that we are only as strong as our weakest link. In some places, antibiotics are used sparingly in the United States are available over the counter. In many countries, a lack of hygiene, sanitation, and basic infection control in medical settings results in increased antibiotic consumption.

If we do not want these superbugs here in the United States, we need to stop them from developing both here and abroad, and we must also improve global surveillance of antibiotic-resistant bacteria and antibiotic consumption. Stopping the spread of antibiotic-resistant bacteria is a global threat, and therefore, solutions must be global in nature.

So I just want to thank the witnesses, look forward to the promising work at each of your agencies and how we in Congress can be your partners in moving forward. And I yield my remaining time to Mr. Green of Texas.

Mr. GREEN. Thank you, Mr. Chairman. Thanks to our ranking member for yielding to me.

As said before, researchers have found a person in the United States carrying bacteria resistance to antibiotics of last resort, an alarming development that could mean the end of the road for antibiotics. For years, scientific leaders across the globe have been warning if we don’t take swift, aggressive action, a post-antibiotic era in which modern medicine we take for granted is no longer safe because we will not be able to control infection from childbirth, in surgery, to dialysis and chemotherapy. Even simple cuts and wounds could be at increased risk of turning fatal without effective antibiotic treatments.

Alarming, at a time when resistance is rising, a pipeline for new antibiotics has dried up. Resistance can and must be slowed,
but it cannot be stopped, and we need new classes of antibiotics to combat drug-resistant antibiotics.

The public value of antibiotics is difficult to overestimate, yet there is a widening acknowledged market fail when it comes to antibiotics. We need meaningful research incentives, strong public-private partnerships, and flexible clinical trials. That is why not only myself but our committee championed the ADAPT Act. It passed in the 21st Century Cures. It would enable the FDA to work with sponsors and reduce regulatory barriers to antibiotic drug development.

ADAPT offers one tool Congress can enact to address the lack of effective treatments against superbugs. I look forward to hearing more about that proposal and other ideas Congress should consider in the ongoing efforts to address this public health crisis.

And again, I will yield back my 14 seconds.

Mr. MURPHY. The gentleman yields back.

I ask unanimous consent that the members' written opening statements be introduced into the record. And without objections, the documents will be entered into the record.

I would now like to introduce the witnesses of our first panel for today's hearing. The first witness on today's panel is Dr. Beth Bell. Dr. Bell is a Director of the National Center for Emerging and Zoonotic Infectious Diseases with the CDC.

We would also like to welcome again Dr. Janet Woodcock. Dr. Woodcock is currently Director of the FDA's Center for Drug Evaluation and Research.

Our third witness on today's panel is Dr. Richard Hatchett. Dr. Hatchett is currently serving as acting director for the Biomedical Advanced Research and Development Authority within HHS Office of the Assistant Secretary for Preparedness and Response.

Our final witness is Dr. Dennis Dixon. Dr. Dixon joins us from the NIAID's Division of Microbiology and Infectious Diseases.

I would like to thank all the witnesses for appearing before the subcommittee today. You are all aware that the committee is holding an investigative hearing, and when doing so has the practice of taking testimony under oath. Do any of you have an objection to taking testimony under oath?

The chair then advises that you are under the rules of the House and the rules of the committee you are entitled to be advised by counsel. Do any of you desire to be advised by counsel during the testimony today?

Seeing no request for that, in that case, will you all please rise, raise your right hand, and I will swear you in.

[witnesses sworn]

Mr. MURPHY. Thank you. All the witnesses have answered in the affirmative, and you are now under oath and subject to the penalties set forth in title 18, section 1001 of the United States Code.

I will have you each give a 5-minute summary of your written statement. Please pay attention to the timing and turn the microphone on and bring it as close to your mouth as you can. Thank you. You may begin, Dr. Bell. You are recognized for 5 minutes.
STATEMENTS OF DR. BETH BELL, DIRECTOR, NATIONAL CENTER FOR EMERGING AND ZOONOTIC INFECTIOUS DISEASE, CENTERS FOR DISEASE CONTROL; DR. JANET WOODCOCK, DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION; DR. RICHARD J. HATCHETT, ACTING DIRECTOR, BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY; AND DENNIS M. DIXON, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH

STATEMENT OF DR. BETH BELL

Dr. Bell. Thank you. Good morning, Chairman Murphy, Ranking Member DeGette, and members of the subcommittee. I am Dr. Beth Bell, director of the National Center for Emerging and Zoonotic Infectious Diseases at the Centers for Disease Control and Prevention. And thank you for the opportunity to testify before you today.

CDC works 24/7 to save lives and protect people against health threats, including the threat of potentially untreatable infections. With support from Congress, CDC is working to improve the Nation’s capacity to detect, respond, and prevent antibiotic-resistant threats in health care settings and across communities to protect Americans and save lives.

Using the resources provided by Congress in fiscal year 2016, CDC is working on four fronts to support transformative improvements in our national capability to identify and respond to antibiotic resistance. First, CDC will invest the largest portion of this funding in our 50 states, six largest cities, and Puerto Rico. CDC will support state activities to improve the detection and prevention of AR infections transmitted across health care and community settings. These are just-in-time investments as the pace and challenges of antibiotic resistance are accelerating and every state needs capacity to take appropriate action.

Second, CDC’s antibiotic resistance lab network will provide infrastructure and lab capacity through seven regional labs across the country. These labs will be able to detect resistant organisms recovered from human samples and new forms of antibiotic resistance. CDC will also provide support for labs in all States to test for CRE, the nightmare bacteria.

Third, CDC’s Advanced Molecular Detection initiative is another important tool in our efforts to identify and solve more outbreaks faster. Because of innovations developed through this AMD initiative, CDC will be able to scale up whole genome sequencing of multiple foodborne pathogens to better understand foodborne antibiotic resistance patterns. Through the National Antimicrobial Resistance Monitoring System, NARMS, sequences from animals, from retail meat, and from humans will be compared to identify new ways of preventing human infections.

Finally, our ability to reduce antibiotic resistance will depend in part on improving antibiotic use, and we are working towards that through better measurement, through expansion of stewardship programs, and through educational campaigns.
The administration’s budget request for fiscal year 2017 includes an increase of $40 million for year 2 of CDC’s Antibiotic Resistance Solutions initiative. And so in fiscal year 2017, in addition to sustaining AR capacity started in ’16, CDC will expand state antibiotic resistance prevention programs to better respond to outbreaks, to improve prescribing, and prevent antibiotic-resistant infections across all health care settings.

These collective investments have a direct impact on the response to AR threats, including the emergence of the MCR–1 gene in the United States. In May, Department of Defense scientists announced the first discovery of the MCR–1 gene in bacteria isolated from a person in the United States. Although there is not an immediate threat to the public or the current health of this patient, this is an important development for the United States. The antibiotic colistin is used as a rescue drug to treat patients with multidrug-resistant infections like CRE.

The MCR–1 gene makes bacteria resistant to colistin. The gene exists on a plasmid, which is a small piece of DNA that is capable of moving from one bacterium to another, spreading antibiotic resistance among bacterial species. The presence of the MCR–1 gene and its ability to share its colistin resistance with other bacteria such as CRE raises the possibility of a bacteria that is resistant to every antibiotic.

USDA also discovered MCR–1 in E. coli isolates collected from two different pig intestines. By comparing the DNA sequences of all three isolates, Federal scientists have determined that the isolates from the pigs are different from that from the human.

Yesterday, CDC issued an alert to proactively notify states, hospitals, and clinical laboratories about the availability of new detection tools for MCR–1 and to reiterate recommendations for infection prevention, environmental cleaning, and reporting to public health.

The identification of MCR–1 vividly illustrates our domestic and global challenges of antibiotic resistance. MCR–1 was first identified in China in November of last year, and in less than 6 months has been identified in a human and two animals in the United States. Antibiotic use anywhere can potentially affect any one of us.

The emergence and reemergence of health threats, including those caused by antibiotic-resistant bacteria, is something we can expect to continue to see in the future. If we lose antibiotics, we could lose the ability to effectively treat sepsis and to provide the care to cancer patients, to organ transplant recipients, or burn and trauma victims.

So thank you again for the opportunity to appear before you today, and I look forward to the opportunity to answer your questions.

[The prepared statement of Beth Bell follows:]
Witness: Beth Bell, MD, MPH

Testimony: House Energy and Commerce Committee, Subcommittee on Oversight and Investigations

Good morning Chairman Murphy, Ranking Member DeGette, and members of the Subcommittee. Thank you for the opportunity to testify before you today on the Centers for Disease Control and Prevention's (CDC's) continued efforts to combat antibiotic resistance, which threatens the United States and modern medicine itself.

CDC is the nation's premier health protection agency, working 24-7 to save lives and protect people against the threat of untreatable infections. We know that, although much effort is being expended to develop new antibiotics, we also must work right now to slow the spread of these resistant bacteria and improve how we use the antibiotics we have.

**Threat of Antibiotic Resistance**

Antibiotic resistance is perhaps the single most important infectious disease threat of our time.

Every year, more than two million people in the United States get infections that are resistant to antibiotics, and at least 23,000 people die as a result. In addition, *Clostridium difficile* (C. difficile), a serious diarrheal infection associated with antibiotic use, causes at least 15,000 deaths every year in the United States.

Modern medicine is at stake. If we lose antibiotics, we lose the ability to effectively treat sepsis and to provide care to cancer patients, organ transplant recipients, and burn or trauma victims. Losing antibiotics would devastate our medical system. In 2014, the President issued an Executive Order directing the development of the National Action Plan for Combating Antibiotic Resistant Bacteria to identify steps Departments across the Federal Government could take to combat antibiotic resistance.

**CDC's Antibiotic Resistance Solutions Initiative**

In fiscal year (FY) 2016, Congress recognized the large and growing threat of antibiotic resistance (AR) and appropriated $160 million to CDC to implement the National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) activities: To detect and respond to resistant pathogens; prevent the spread of resistant infections; and collaborate with partners to
encourage innovation for new prevention strategies. These resources are transforming how our
nation tackles and slows antibiotic resistance comprehensively, efficiently, and systematically.

With support from Congress, CDC is working with Federal, state, and local public health,
academic, healthcare, and veterinary partners to: improve capacity to detect and respond to AR
threats in healthcare and communities, protect patients, and save lives. CDC will invest the
largest extramural portion of this funding in the 50 state health departments, the six largest local
health departments, and Puerto Rico. This Antibiotic Resistance Solutions Initiative will support
comprehensive and coordinated public health action to minimize the spread of antibiotic
resistance across states, counties, and cities.

DETECT AND RESPOND

This public health investment opens a new chapter against antibiotic resistance, improving state
health department healthcare-associated infection (HAI) and AR detection capacity so they can
better detect resistance and respond to outbreaks faster. Beginning this fall, CDC’s Antibiotic
Resistance Lab Network will provide infrastructure and lab capacity through as many as eight
regional labs across the country. These labs will be able to detect resistant
organisms recovered from human samples and new forms of antibiotic resistance—including
mutations that allow bacteria to withstand last-resort drugs like colistin—and report these
findings to CDC as well as back to facilities and states. These efforts will generate better data
for stronger infection control to contain current threats and prevent future resistance threats.

CDC is particularly concerned about carbapenem-resistant Enterobacteriaceae (CRE)—often
referred to as the nightmare bacteria—and emerging multidrug-resistant organisms. In addition
to building on existing HAI/AR state programs, CDC will provide support for labs in all states to
test for CRE and support regional labs for additional testing in outbreak response (e.g.,
screening colonized patients). The Emerging Infections Program (EIP), a national resource for
surveillance, prevention, and control of emerging infectious diseases, will also build on
population-based detection of all invasive Staphylococcus aureus (including MRSA),
carbapenem-resistant Pseudomonas, and ESBL-producing Enterobacteriaceae.

CDC’s advanced molecular detection (AMD) initiative is another important tool in our efforts to
identify and address antibiotic resistance. The expansion of whole genome sequencing into
public health surveillance activities represents a paradigm shift that has already saved lives by
identifying and solving more outbreaks, faster. For example, CDC is using AMD to better
characterize Listeria bacteria in foodborne disease outbreaks. Earlier this year, whole genome
sequencing was used in a multi-state *Listeria* outbreak associated with packaged salads; this technology confirmed that cases identified in Canada were closely related. CDC will scale up whole genome sequencing of multiple foodborne pathogens—including *Salmonella*, *Shigella*, and *Campylobacter*—to better understand foodborne AR patterns. CDC will also use the National Antimicrobial Resistance Monitoring System (NARMS) and work with the Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) to sequence foodborne pathogens to identify new ways of preventing human infection associated with resistant bacteria in food animals. Finally, CDC will provide states with additional epidemiologic support for foodborne investigations to ensure rapid response to new illness reports and outbreaks of resistant infections identified through this new testing.

**PREVENT**

CDC’s Antibiotic Resistance Solutions Initiative will help slow resistance and protect the antibiotics we have today with active coordination of care across communities, data collection, and stewardship program implementation. State HAI/AR Prevention Programs will work with healthcare facilities in up to 25 states to scale up this coordinated approach to prevent the transmission of multidrug-resistant organisms and *C. difficile* across communities.

Our ability to reduce antibiotic resistance will depend in part on improving antibiotic use, and we are working toward that through better measurement of antibiotic use, expansion of stewardship programs, and support for educational campaigns. CDC is working with large healthcare systems to demonstrate best practices in stewardship programs using CDC’s Core Elements of Antibiotic Stewardship and measure antibiotic use outcomes. Using electronic data through the National Healthcare Safety Network’s (NHSN’s) antibiotic use module, we can assess appropriate use and target interventions in and across healthcare settings. These data will inform how facilities can improve antibiotic use and reduce resistance. CDC is collaborating with partners including the Centers for Medicare & Medicaid Services (CMS), Quality Improvement Networks (QINs), and CMS’s Center for Medicare and Medicaid Innovation (CMMI) to implement effective stewardship programs.

Much of this work in turn responds to the threat of sepsis, often a sign of severe infection that can include resistant infections. CDC is committed to preventing infections that lead to sepsis and promoting early recognition of sepsis across medical care.
Finally, CDC will also work with FDA and USDA to ensure that practicing veterinarians have the tools, information, and training to prevent drug resistance by promoting responsible use of antibiotics in animals, including those animals consumed by humans.

**INNOVATE**

CDC’s Antibiotic Resistance Solutions Initiative will accelerate prevention innovation, giving us new tools to slow the threat of resistance. Through the Prevention Epi-Centers and other innovation partners, CDC is able to address questions and gaps in knowledge related to resistant infections. CDC is also performing intramural studies and supporting extramural studies to better understand the microbiome and how its disruption influences an individual’s risk for developing an antibiotic resistant infection. This work could help in tailoring prevention and antibiotic stewardship programs and uncovering new therapies that restore the healthy microbiome, reducing the risk of AR infections.

**COLLABORATE**

CDC is working with state, Federal, and international partners to align AR activities and maximize the effectiveness of funding. For example, CDC’s efforts in whole genome sequencing for foodborne AR infections will involve collaborations with the FDA, USDA, and the National Institutes of Health (NIH) to track how antibiotic resistant genes in pathogenic and commensal bacteria that may be impacting humans, food, and animals. CDC, NIH, and the Department of Defense (DoD) are working together on when and how to best use whole genome sequencing to solve CRE outbreaks. CDC is collaborating with FDA on supporting and expanding use of the AR Isolate Bank, including coordinating efforts to generate genomic sequence data for all isolates in the AR Isolate Bank, which supports industry and academic partners working to develop new treatments and diagnostics.

**Additional Investments**

The Administration’s budget request for FY 2017 includes an increase of $40 million for year two of CDC’s Antibiotic Resistance Solutions Initiative. This increase will build on AR capacities started in FY 2016, allowing CDC to expand the nation’s ability to detect, respond to, and prevent AR infections across healthcare settings and in the community.

In FY 2017, in addition to sustaining AR capacities started in FY 2016, CDC will expand the State HAI/AR Prevention Programs in up to 50 states, six large cities, and Puerto Rico to better respond to outbreaks, improve prescribing, and prevent AR infections across all healthcare settings.
settings (e.g., inpatient, outpatient, and long-term care settings). CDC will also further expand state public health laboratory capacity in up to 50 states, six large cities, and Puerto Rico to rapidly screen enteric bacteria for resistance and ensure the nation’s ability to rapidly detect and investigate AR threats across the country and in more enteric pathogens, specifically Campylobacter and Shiga toxin-producing E. coli.

These collective investments have a direct impact on the public health response to the AR threat, including our continued response to new threats, such as the emergence of the mcr-1 gene, reported in November of 2015 in China.

**Public Health Response to Discovery of mcr-1**

The antibiotic colistin is used as a last-resort drug to treat patients with multidrug-resistant infections, including CRE. The mcr-1 gene makes bacteria resistant to colistin. The gene exists on a plasmid, a small piece of DNA that is capable of moving from one bacterium to another, spreading antibiotic resistance among bacterial species. CDC and Federal partners have been hunting for this gene in the U.S. since its emergence in China was reported in 2015.

Following the identification of mcr-1 in China, CDC, FDA and USDA began searching for mcr-1 in bacterial samples taken from human, retail meat, and food animal sources. This work is facilitated by the National Antimicrobial Resistance Monitoring System (NARMS), which has detected emerging resistance to clinically important antibiotics for the past 20 years. NARMS is a partnership among FDA, USDA, CDC, and state and local public health departments that tracks changes in the antimicrobial susceptibility of intestinal bacteria. Through NARMS, the USDA discovered mcr-1 in an E. coli isolate collected from a pig intestine. The DNA sequence of that isolate revealed that the strain contained the mcr-1 gene on a plasmid. USDA scientists also determined that the mcr-1 carrying colistin-resistant E. coli from intestinal content of a pig was resistant to other antibiotics, including ampicillin, streptomycin, sulfisoxazole, and tetracycline. The resistance to these other antibiotics was not on the plasmid carrying the mcr-1 gene. Preliminary analysis by USDA’s Agricultural Research service indicates that the bacterial strain is E. coli 0160:H40. An isolate from a second pig is undergoing analysis. As of April 2016, more than 55,000 genome sequences of several types of bacteria from humans, retail meat, and food animals have been screened through NARMS. All were negative for the mcr-1 gene. NARMS continues to look for this gene.

In addition, CDC investigated bacterial genomes and used a highly sensitive testing method known as polymerase chain reaction, or PCR-screening, to look for the mcr-1 gene among
healthcare-associated pathogens. In this effort, CDC screened 735 genomes, including 690 Enterobacteriaceae (e.g., carbapenem-susceptible Enterobacteriaceae (CSE) and carbapenem-resistant Enterobacteriaceae (CRE)) and 45 non-Enterobacteriaceae (e.g., Pseudomonas and Acinetobacter) from the surveillance, outbreak, and special study and reference collections. All these human isolates were negative for mcr-1 using this PCR screening method.

In May 2016, DoD scientists announced the first discovery of the mcr-1 gene in bacteria isolated from a person in the United States. CDC is currently part of the coordinated public health response to DoD's identification of the gene in E. coli bacteria in a urine sample from a Pennsylvania woman with no recent travel outside of the country. The isolates identified from the 1st pig is different from the isolate identified in the human case; the isolate from the 2nd pig is currently undergoing analysis.

The DoD finding of the mcr-1 gene in bacteria from a person started an ongoing public health investigation led by CDC and the Pennsylvania Department of Health. Although only one human isolate has been recovered in the United States to date, CDC takes this finding very seriously and is working with DoD, the Pennsylvania Department of Health, local health departments, and others to identify people who have had contact with the Pennsylvania patient. The investigation is currently focused on identifying and screening close contacts, including household and healthcare contacts of the Pennsylvania patient to determine whether any of them might carry bacteria containing the mcr-1 gene.

Despite some media reports, the Pennsylvania Department of Health investigation has determined that the woman did not have CRE, and the bacteria identified is not resistant to all antibiotics (referred to as a pan-resistant infection). The presence of the mcr-1 gene, however, and its ability to share its colistin resistance with other bacteria, such as CRE, raises the possibility that pan-resistant bacteria could develop.

The transformative improvements being implemented across the country through CDC's Antibiotic Resistance Solutions Initiative will greatly expand and strengthen national efforts to identify and respond to this gene if it is circulating.

**Conclusion**

The emergence and reemergence of health threats, including those caused by antibiotic resistant bacteria, is something we can expect to continue to see in the future. Consistent with the *National Action Plan for Combating Antibiotic-Resistant Bacteria*, CDC and other government agencies continue to track the emergence of antibiotic resistance. CDC is working
to strengthen the nation's ability to respond rapidly and effectively, protecting Americans and the precious antibiotics we need to fight deadly bacteria.

Thank you again for the opportunity to appear before you today. I appreciate your attention to the antibiotic resistance threat, and I look forward to answering your questions.
Mr. Murphy. Thank you. Dr. Woodcock, you are recognized for 5 minutes.

STATEMENT OF DR. JANET WOODCOCK

Dr. Woodcock. Thank you for holding a hearing on this critical topic.

FDA is involved in many fronts in the fight against resistant organisms. We're participating actively in the CARB initiative and collaborating internationally and also of course with our Federal partners represented here. Our Center for Veterinary Medicine oversees animal drugs. They have received commitments from the manufacturers are medically important antibiotics to submit supplements by the end of the year. As a result of this, these drugs will have to be prescribed by a veterinarian and can't be used for growth promotion purposes.

Our Center for Devices and Radiologic Health regulates in vitro diagnostics or test kits, including antimicrobial susceptibility tests and diagnostics. They're seeing a growing pipeline of rapid diagnostic tests under development. This is very good news. These tests are intended to identify if a person has a bacterial infection or—versus a virus or has bacteria circulating in the blood or even rapidly diagnose certain types of resistant organisms. So we hope these development programs are successful.

They also plan to issue guidance on what they call coordinated development of susceptibility tests. So as we have new antimicrobials approved by Center for Drugs, we could have susceptibility tests also available that could be interpreted by clinicians.

Our Center for Biologics regulates vaccines. We know that prevention is a best approach to disease, and of course there are some vaccines for microbial diseases, and we would hope that more are going to be developed.

The Center for Drug Evaluation and Research that I head regulates antimicrobials. We've seen the percent of infections treated by common antibiotics shrink over time, as everybody's been saying, as resistance grows. CDER's been actively implementing the GAIN Act that Congress passed several years ago. We've granted 107 qualified infectious disease product designations to 63 different molecules. The designated products can receive fast-track designation, and they get a priority review. On approval, they receive additional 5 years of market exclusivity, so this is an incentive of course. Five designated antibacterial drugs and one antifungal drug have been approved since GAIN was enacted.

We continue to work on streamlining drug development. We've issued guidelines. We're trying to lower the barriers, but many of the barriers, as I'm sure we'll discuss, are either scientific or economic barriers to new antimicrobials.

Now, there are further efforts going on in lowering the barriers. I really commend BARDA who is exploring the use of a master common protocol. We're working with them, novel ways of studying these that lower the barriers and make some types of studies actually feasible.

The 21st Century Cures bill that was passed in the House contains provisions for the limited population use provision, and the
Senate PATH Act does mirror that. We're also very interested in the issue of antimicrobial break points and the use of a more rapid and agile method for changing the break point designations. Finally, though, drug development in this area remains fragile and weak. The incentives that have been put in place apparently are not enough to overcome the scientific challenges that the industry faces in finding new targets and developing these and then actually making money on them. Much more needs to be done, I think, to address this threat across all the groups represented here, but the drug development area in particular needs further examination.

Thank you.

[The prepared statement of Janet Woodcock follows:]
DEPARTMENT OF HEALTH AND HUMAN SERVICES

STATEMENT OF

JANET WOODCOCK, M.D.
DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
COMMITTEE ON ENERGY AND COMMERCE
U.S. HOUSE OF REPRESENTATIVES

“EXAMINING WAYS TO COMBAT ANTIBIOTIC RESISTANCE AND FOSTER NEW DRUG DEVELOPMENT.”

JUNE 14, 2016

RELEASE ONLY UPON DELIVERY
INTRODUCTION

Mr. Chairman, Ranking Member DeGette, and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss the current state of antibiotic resistance and the need for new solutions to the current crisis.

To address the growing public health concern, on September 18, 2014, the Administration released the National Strategy for Combating Antibiotic-Resistant Bacteria (CARB), and President Barack Obama signed Executive Order 13675, which called for creation of a National Action Plan and established a Federal Task Force to draft and implement the action plan. FDA is actively engaging in these efforts in coordination with other Federal agencies.

The decline in antibacterial drug research and development (R&D) in the private sector, at a time when serious antibiotic resistant infections are on the rise, is a tremendous public health problem, resulting in a very serious unmet medical need. According to the Centers for Disease Control and Prevention (CDC), each year in the United States, at least two million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a result of these infections.

Antibacterial drugs are critically important across medicine, including in the care of premature infants and for use in surgery, chemotherapy, and organ transplantation. However, bacteria are adept at becoming resistant to antibacterial drugs, as highlighted by the recent identification of a patient in Pennsylvania infected with *E. coli* bacteria possessing the *mcr-1* gene. It is essential to
use antibiotics judiciously to slow the development of resistance. Moreover, new antibacterial drugs are needed to provide treatment options in cases where resistance has eroded the effectiveness of existing drugs.

The Challenges Impacting Antibacterial Drug Development

There are significant scientific and economic challenges impeding the development of new antibiotics. From a scientific standpoint, many patients with bacterial infections are very sick and need to begin antibiotic therapy immediately. However, enrolling a very sick patient in a clinical trial in order to evaluate new antibiotics at the same time they are very sick can be difficult because critically ill patients may be unable to provide informed consent.

From an economic standpoint, antibiotics are generally viewed as less profitable by companies and venture capitalists because of their relatively low price and because they are generally taken only for a short period of time and often only for one course of treatment by any given patient. Compare this to the long, dependable income stream from a diabetes medicine or a blood pressure medicine that patients often take for the rest of their lives, or the relatively high price associated with cancer and some antiviral drugs. These economic realities can make it challenging for a company to justify large expenditures for the development of drugs in this area, as a report from the Eastern Research Group (ERG), funded jointly by HHS Office of the Assistant Secretary for Planning and Evaluation (ASPE) and FDA, affirms.¹

Furthermore, the inappropriate use of antibacterial drugs can accelerate the development of antibiotic resistance. It is essential that we use antibacterial drugs prudently in order to preserve the effectiveness of these drugs. The ability of drug resistance to be transferred from one bacteria to another and spread among a population of patients is a phenomenon unique to infectious diseases. Judicious use of antibacterial drugs is essential, in both the human and animal sectors.

**Use of Common Clinical Trial Protocols to Encourage Antibacterial Drug Development**

A promising strategy for encouraging antibacterial drug development is the establishment of a clinical trial network that can operationalize common clinical trial protocols at a level of quality that matches the pharmaceutical industry and that can respond to future needs in an agile fashion. The quality of the network should be at a level where pharmaceutical companies welcome the opportunity to perform their core development program utilizing the common protocols that are housed within the clinical trial network. Such a clinical trial network would allow pharmaceutical companies to utilize shared expertise and infrastructure to study antibacterial drugs. The CARB calls out this specific approach to reducing obstacles faced by drug companies developing new antibacterial drugs and states that the U.S. Government will examine the feasibility of generating and applying master clinical protocols to multiple test groups of patients while sharing a common control group. Colleagues at the Office of the Assistant Secretary for Preparedness and Response’s Biomedical Advanced Research and Development Authority (BARDA) recently published a request for information on an antibacterial drug clinical trial network to gather information to evaluate the costs and practical considerations involved in establishing such a network.
What FDA is Doing to Address the Current Challenges

Provisions in a law passed in 2012, commonly known as the Generating Antibiotics Incentives Now Act, or the GAIN Act, are helping to stimulate the development of new antibiotics. Under GAIN, certain antibacterial or antifungal drugs intended to treat serious or life-threatening infections can be designated as “Qualified Infectious Disease Products” (QIDPs). As part of its QIDP designation, a drug receives priority review and is eligible for fast-track designation. At the time of approval, a product with QIDP designation qualifies for an additional five years of marketing exclusivity, to be added to certain existing exclusivity periods under the Federal Food, Drug, and Cosmetic Act. To date, FDA has granted 107 QIDP designations for 63 different unique molecules.

Since GAIN was passed, FDA has approved five new antibacterial drugs and one new antifungal drug with the QIDP designation. Three of the five antibacterial drugs, Dalvance (dalbavancin), Orbactiv (oritavancin), and Sivextro (tedizolid phosphate), are intended to treat acute bacterial skin and skin-structure infections (ABSSSI) caused by methicillin-resistant Staphylococcus aureus and certain other types of bacteria. Zerbaxa (ceftolozane/tazobactam) is indicated for the treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal

---

2 Priority-review designation directs overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions or for drugs that have a QIDP designation. Priority-review designation does not affect the length of the clinical trial period. FDA informs the applicant of a priority-review designation within 60 days of the receipt of the original BLA, NDA, or efficacy supplement.

3 Fast-track designation is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. Once a drug receives fast-track designation, early and frequent communication between the FDA and a drug company is encouraged throughout the entire drug development and review process.
infection (cIAI). Avycez (ceftazidime/avibactam) is indicated for cUTI and cIAI for patients who have limited or no alternative treatment options.

FDA is working hard to streamline requirements for clinical trials for studying new antibacterial drugs, and the provisions of the GAIN Act are being actively implemented, but much more is needed. There are still significant economic and scientific challenges in the development of new antibacterial drugs that need to be addressed. Additional approaches to reducing the costs of studying antibacterial drugs, such as common clinical trial protocols, could provide other important means to stimulate antibacterial drug development. We also need cutting-edge science to move forward the development of new and innovative antibacterial drugs, as well as alternative therapeutics to combat bacterial infections.

To help drive this effort, FDA is working with academia, regulated industry, professional societies, patient advocacy groups, and government agencies to advance the science of clinical trials for antibacterial drugs. For example, FDA has contributed to the efforts of the Biomarkers Consortium of the Foundation for the National Institutes of Health (FNIH) to develop new endpoints for studying antibacterial drugs. FDA also works closely with the Clinical Trials Transformation Initiative (CTTI), a key group of dedicated scientists focused on streamlining and advancing clinical trials for more efficient drug development. FDA and CTTI have partnered to initiate activities related to efficient design and conduct of clinical trials for testing new antibiotics. FDA has also teamed up with colleagues at the Brookings Institution’s Engelsberg Center for Health Care Reform and more recently the Duke-Margolis Center for Health Policy to galvanize the scientific community’s efforts in new antibiotic drug
development. The first Brookings Council for Antibacterial Drug Development (BCADD) meeting was held in August 2012, and the Brookings Institution has continued to convene meetings focused on a range of antibacterial drug development issues.

As part of these collaborative efforts, FDA will conduct a two-day public workshop in July 2016 focused on facilitating antibacterial drug development for patients with unmet needs and developing antibacterial drugs that target a single species. Discussions will focus on potential development pathways, aspects of clinical trials including which patient populations to study, trial designs and endpoints, and the role of clinical trial networks in antibacterial drug development.

Encouraging the Development of New Antibacterial Drugs
Given the public health threat posed by antimicrobial resistance, it is necessary to consider new mechanisms for encouraging the development of new antibacterial drugs to address unmet medical needs in the treatment of serious and life-threatening bacterial infections. We look forward to ongoing engagement with consumers, clinical experts, researchers, industry, and others to achieve this goal.

As the Committee knows, one option that has been proposed is the establishment of a new Limited Population Antibacterial Drug (LPAD) program. It is our understanding that, as a general matter, drugs approved using an LPAD pathway would be based on more streamlined development programs that establish that the drug is safe and effective in a limited population of patients with serious or life-threatening infections and unmet medical needs.
Importantly, because LPAD drugs would be approved based on streamlined development programs, there would be more uncertainty about potential risks posed by the product. This may result in a positive benefit-risk profile in a limited population of patients with serious or life-threatening infections and unmet medical needs. However, the benefit-risk assessment would be different for a broader, more heterogeneous patient population with less serious manifestations of the infection and which has other treatment options. This distinction should be clearly conveyed to the provider community. A clear branding mechanism would convey accurately to physicians using the product the limitations of the data supporting approval, including the uncertainty and the unique benefit-risk profile associated with the drug. Such labeling is particularly important in the context of antibiotic drugs, where historical overuse has led to increased antimicrobial resistance.

**Accelerating Development of Rapid Diagnostic Tests for Antibiotic Resistance**

Rapid diagnostic tests are an essential component of combating antibiotic resistance. Specific goals for accelerating the development of these rapid diagnostics are identified in the CARB. Rapid diagnostics can aid in faster diagnosis of patients with antibiotic resistant infections and result in appropriate therapy being initiated earlier. Rapid diagnostics also serve an important role in identifying patients colonized with resistant isolates at entry to hospitals, such that patients can be isolated and transmission to other patients minimized. Perhaps even more importantly, rapid diagnostics may aid in differentiating viral infections from bacterial infections and substantially reduce the use of unnecessary outpatient antibiotic therapy.
Through release of guidance documents and several public workshops, FDA and industry have made great progress in this area, however, similar to drug development, there are significant challenges to the development and use of diagnostics relative to empiric antibiotic use. Strategies to incentivize development and use of new antibacterial drugs have similar parallels for diagnostics.

**Expedited Updating of Susceptibility Test Interpretive Criteria (Breakpoints) To Maximize the Effective Use of Antimicrobial Products**

Enabling physicians to select appropriate antibacterial drugs is critical to individual health, as well as the public health, as we continue to combat antimicrobial resistance. Generally, physicians rely on antimicrobial susceptibility test (AST) devices, which provide information about whether a bacterium is either susceptible or resistant to an antibacterial drug. The criteria used to determine susceptibility are commonly referred to as “breakpoints.” This information helps physicians choose appropriate antibacterial drugs for treatment. The results of such testing is also important to identify patients with certain resistant bacteria that warrant additional infection control measures to prevent spread of their resistant bacteria to others.

Outdated breakpoints can cause numerous problems, such as interfering with the implementation of appropriate infection control procedures, which can increase the chances that problematic resistant bacteria can be spread to others. Hospitals need up-to-date breakpoint information in order to determine whether an infection is caused by a resistant pathogen, and to put appropriate infection control procedures in place for those antibiotic-resistant bacteria.
AST device manufacturers need to be able to incorporate up-to-date breakpoint information into their devices quickly. However, currently, it can take several years to do so. Under the current regulatory framework, each antibacterial drug manufacturer updates its drug labeling with new breakpoint information and only then does each device manufacturer update its device algorithms and labeling. Reviewing breakpoint labeling supplements for each individual drug product (even when it shares the same active ingredient(s), and thus, generally has the same breakpoints) is no small task. Moreover, the process begins with the submission of labeling supplements from the drug manufacturers.

This protracted process of manufacturers updating the product labeling for each antimicrobial drug product adversely affects the public health by delaying AST device manufacturers from being able to promptly update the breakpoint information in their devices. It utilizes both industry and Agency resources that could otherwise be used for antibacterial and antifungal drug development or reviews that could confer greater benefits for patients. We need a better, more modern and streamlined process to help AST device manufacturers incorporate up-to-date and comprehensive breakpoint information in their devices more quickly, in order to get this information to health care providers sooner for the care of patients.

**Solution for Updating Breakpoint Information Faster**

In order to address the problems with the current scheme for updating breakpoints, we need to take breakpoints out of the drug product label and utilize more rapid, electronic means of communicating this information. Posting breakpoint information on FDA’s website could enable us to update breakpoint information more efficiently. As mentioned, many antibacterial drugs
have the same active ingredient(s), and thus the same breakpoints. Accordingly, as a general matter, breakpoints are neither proprietary, nor specific to a particular drug product. Therefore, if FDA posted appropriate breakpoints for penicillin or amoxicillin products on the Internet, then FDA could take one single action to update the breakpoints for multiple drug products with the same active ingredient simultaneously.

To help FDA ensure that it can update breakpoint information accurately and expeditiously, the Agency could leverage the work being done by standards-development organizations that develop breakpoints, and recognize them, when FDA agrees that they are appropriate. FDA would retain full authority to accept a standard in whole or in part, or to establish alternative breakpoints. In addition, companies could submit data to support alternative breakpoints, if they disagree with the recognized standard.

CONCLUSION

It is virtually undisputed that we are facing a public health crisis because of the rise of serious resistant infections and the simultaneous decline in R&D in this area. FDA is using the tools we have to begin to strengthen the antibiotic drug pipeline. However, more work is needed to improve the current climate, and FDA is looking forward to continuing to work with stakeholders to address this public health crisis.

I am happy to answer any questions you may have.
Mr. MURPHY. Thank you, Dr. Woodcock.
I now recognize Dr. Hatchett for 5 minutes.

STATEMENT OF DR. RICHARD J. HATCHETT

Dr. HATCHETT. Good morning, Chairman Murphy, Ranking Member DeGette, and members of the committee. Thank you for inviting me to testify about our efforts to combat antibiotic-resistant bacteria. I am Dr. Richard Hatchett, acting director of the Biomedical Advanced Research and Development Authority within the Office of the Assistant Secretary for Preparedness and Response. BARDA was established in December 2006 to support the advanced research development and procurement of medical countermeasures against chemical, biological, radiological, and nuclear threats, pandemic influenza, and emerging diseases such as Ebola and Zika.

In 2010, BARDA initiated its Broad Spectrum Antimicrobials program, or the BSA program that I will refer to, and in 2016, Congress awarded BARDA substantial new funding specifically to combat antibiotic-resistant bacteria. The BSA program was established to support the development of new classes of antibiotics for both biodefense and commercial applications. Under the auspices of the program, we now manage seven public-private partnerships and a pipeline of nine antibacterials.

BARDA’s objectives have been to revitalize the antibiotic pipeline, emphasize programs that address the immediate public health threat of multidrug-resistant organisms, and enhance our biodefense capabilities. We have achieved notable success. Our portfolio is quite mature at this point. Five BARDA products are in phase 3 clinical development, and two have completed the pivotal studies required for FDA approval.

Several products show promise for the treatment of infections due to carbapenem-resistant Enterobacteriaceae or CRE, one of the most urgent threats that we face, and a few have shown in vitro activity against bacteria harboring the MCR–1 colistin-resistance gene recently identified in a patient in Pennsylvania.

And we are working with our international partners. One of our partnerships has facilitated groundbreaking coordination of funding with the EU’s Innovative Medicines Initiative to speed the development of a drug called aztreonam-avibactam.

BARDA also supports the development of improved clinical diagnostics. Without better diagnostics to guide antibiotic therapy, it will be difficult to prevent the emergence of resistant bacteria. BARDA would thus support a diverse set of tools to differentiate viral and bacterial infections, identify resistant infections in the physician’s office, and measure antimicrobial susceptibility. BARDA aims to simplify genetic sequencing tools so that they can be used in clinical laboratories for the evaluation of resistant infections.

Finally, BARDA and NIH will offer a $20 million prize for the development of truly novel diagnostics for drug-resistant bacteria. We will be announcing more details about this prize later this year.

To achieve these goals, BARDA employs innovative partnership models. Within HHS, BARDA has pioneered the use of portfolio partnerships that can advance multiple drug candidates simulta-
neously. BARDA has established these flexible cost-sharing business partnerships using our other transaction authority. We have found that portfolio-based funding reduces risk by allowing for the reallocation of resources across activities and among drug candidates as technical and business risks materialize.

Clearly, the early-stage antimicrobial pipeline is too thin. To enrich it, BARDA and NIAID are working together to establish an initiative we are calling the CARB accelerator. Innovation frequently occurs in small biotechnology companies and in academic laboratories with limited resources and expertise to move product candidates forward. In such circumstances, promising early-stage candidates often fail to advance. The accelerator will serve as an incubator for new products and explicitly seeks to improve success rates in the early-stage antibiotic pipeline.

BARDA will launch the accelerator in 2016 and support the program for at least 5 years while NIAID will provide an array of product development support services. Both entities will collaborate in managing the program and its investments through a joint oversight committee. Stay tuned. We certainly will have a lot more to report on this initiative in coming years.

In summary, as new forms of antibiotic resistance continue to spread worldwide, the prospect of bacterial strains resistant to all available antibiotics can no longer be ignored. Developing new tools for diagnosing and treating drug-resistant bacteria will be essential to preserving the practice of modern medicine.

ASPR and its partners play a critical role in leading the charge against such threats, and we look forward to working with Congress to address the global challenge of antimicrobial resistance. I look forward to addressing your questions.

[The prepared statement of Richard J. Hatchett follows:]
Written Testimony
House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations

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

Statement of
Richard J. Hatchett, MD
Acting Deputy Assistant Secretary and Acting BARDA Director
Office of the Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 10:00 a.m.
June 14, 2016
Good morning, Chairman Murphy, Ranking Member DeGette, and Members of the Committee.
Thank you for the opportunity to testify before you today about our government’s efforts to combat antimicrobial-resistant bacteria. I am Dr. Richard Hatchett and I serve as the Acting Director of the Biomedical Advanced Research and Development Authority (BARDA), a component of the Office of the Assistant Secretary for Preparedness and Response (ASPR) in the U.S. Department of Health and Human Services (HHS). In this capacity, I also serve as the Acting Deputy Assistant Secretary for Preparedness and Response.

BARDA was established by the Pandemic and All-Hazards Preparedness Act (PAHPA) in December 2006 to support the advanced research, development and procurement of novel and innovative medical countermeasures such as vaccines, antimicrobial drugs, and medical devices (including diagnostics) to address the medical consequences of chemical, biological, radiological, and nuclear (CBRN) agents of terrorism and naturally-occurring and emerging threats, such as the 2009-H1N1 influenza, H7N9 influenza, Ebola, and Zika viruses. Through the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE), ASPR is working on efforts to address the growing threat of antimicrobial resistance, which has expanded in recent years. I appreciate the opportunity to highlight our progress to-date and underscore the significant challenges remaining.

BARDA works with our HHS and other federal agency PHEMCE partners to transition medical countermeasures from early development into advanced development and ultimately to an application for Food and Drug Administration (FDA) regulatory review and approval. Advanced development includes critical steps needed for a product to be ready for use. This involves
optimizing manufacturing processes so products can be made in quantity to scale, creating and optimizing assays to assure product integrity, conducting late-stage clinical safety and efficacy studies, and carrying out pivotal animal efficacy studies that are often required for approval. Since 2006, BARDA has managed the advanced development of nearly 150 medical countermeasures for CBRN threats and pandemic influenza. Six of these products have received FDA approval in the last two years alone.

Today, we face a growing threat that has the potential to impact more Americans than an infectious disease outbreak or terrorist attack with a biological agent. Antibiotics and other antimicrobial agents have been effective in treating common infections since their widespread use in the 1940s. They are essential to the practice of modern medicine. The problem of antimicrobial resistance was recognized shortly after the first antibiotics, the sulfonamides, were introduced in the late 1930s, and has always presented concerns. Historically, when an infection demonstrated resistance to one class of antibiotics, clinicians would simply switch to a different class. However, the past two decades have witnessed a significant increase in the spread of organisms resistant to multiple classes of antibiotics. Compounding the problem, the pace of introductions of new antibiotics has slowed considerably largely because there is not a sufficient private sector incentive to invest in antibiotic development.

Gram negative bacteria, in particular, have become increasingly resistant to available antimicrobial drugs, and deadly and extremely difficult-to-treat pathogens such as carbapenem-resistant Enterobacteriaceae (CRE) have become more widespread. Colistin, which has long been considered a drug of last resort due to its serious side effects, is being used increasingly to
treat infections with such bacteria. The recent emergence of a plasmid-borne colistin resistance gene, \textit{mcr-1}, thus portends the emergence of truly pan-drug resistant bacteria, for which no current antibiotics are effective. The report three weeks ago of \textit{mcr-1}-carrying \textit{E. coli} in a patient with a urinary tract infection in Pennsylvania starkly highlights the urgent need for proactive action to combat antimicrobial resistance.

Along with our PHEMCE colleagues, BARDA has worked aggressively over the last six years to meet this threat and to re-engage academia and industry in the development of new antibiotics and antiviral drugs. Consistent with an ASPR strategic priority to invest in biodefense products and technologies, which also support everyday applications, BARDA’s development of new antibiotics and antiviral drugs is critical to our defense from a naturally occurring threat or terrorist attack. It also has the potential for substantial day-to-day benefit for health care across the U.S. In 2010, BARDA established a Broad Spectrum Antimicrobial (BSA) program to support the development of new classes of antibiotics. Over time we have built out our portfolio and now manage a pipeline of nine products.

BARDA’s objectives in establishing the BSA program were to: (1) revitalize the antibacterial pipeline through the support of public-private partnerships targeting novel unprecedented and precedent classes of antibiotics; (2) emphasize programs that address the immediate public health threat of multidrug resistant strains of hospital and community acquired pathogens; (3) provide a biodefense capability to bridge the response between the first clinical case of threat agent infection to when mass dispensing of medical countermeasures is initiated; and (4) enable
the evaluation of products for all biothreat pathogens via the development of animal models and tools to support regulatory approval.

We have achieved notable successes in this area. We have built a robust portfolio of broad spectrum antibiotics that possess activity against Gram negative bacteria, which is noteworthy given the limited number and increasing ineffectiveness of antibiotics against these deadly and difficult-to-treat bacteria. Five of our programs have reached Phase 3 clinical development, the last stage before an application for FDA approval, and two products have completed the pivotal registration clinical studies required for approval. One relationship, with Astra Zeneca, is noteworthy in that it reflects a groundbreaking effort to coordinate funding with the EU’s Innovative Medicines Initiative (IMI) and thereby speed the development of Astra Zeneca’s lead antibiotic, aztreonam/avibactam.

In 2014, the President’s initiative on Combating Antibiotic-Resistant Bacteria (CARB) directed BARDA to “develop new and next-generation countermeasures that target antibiotic-resistant bacteria that present a serious or urgent threat to public health” through our advanced development of both drugs and diagnostics.

As outlined in the companion National Strategy and Action Plan for CARB, PHEMCE partners were given clear goals for addressing antimicrobial resistance, objectives for meeting those goals, and milestones to measure progress and success. ASPR, in cooperation with its federal partners, has been engaged in laying out a strategy to address the medical consequences of antimicrobial resistance. Within HHS, we are engaged in strategic advisory boards and working groups dedicated to addressing many of the requirements in the national action plan such as the
Interagency Task Force on Antimicrobial Resistance, the Transatlantic Taskforce on Antimicrobial Resistance, and the National Strategy for Research and Development working group.

The recent identification of an mcr-I-carrying *E. coli* bacteria in a patient with a urinary tract infection in Pennsylvania highlights the serious health threat posed by drug-resistant bacteria. The nine antibacterial products that BARDA is developing address a range of drug-resistant bacterial threats, including *E. coli*, that were identified as either urgent or serious by the CDC in their 2013 report on the public health crises of antibiotic-resistant infections. A number of these have shown promise for the treatment of infections due to carbapenem-resistant Enterobacteriaceae (CRE). A few of the drugs in BARDA’s portfolio have already shown direct *in vitro* activity against bacteria harboring *mcr-I* (so-called “superbugs”) and if approved these products could provide some relief from resistance concerns in the future. More broadly, each of the products in the BARDA portfolio is a broad spectrum antibiotic that possesses activity against Gram negative bacteria, which is important because comparatively few antibiotics active against Gram negative bacterial infections are in development and new drugs to treat such infections are desperately needed. BARDA is actively working with industry to pursue innovate approaches and strategies to improve our nation’s arsenal against antibiotic resistant organisms.

Combating antibiotic resistance is a public health and national security priority, and BARDA has developed a number of innovative partnership models to support this goal. In recent years, BARDA has pioneered the use of portfolio partnerships, in which companies investigate the advancement of multiple drug candidates at the same time. Funding a portfolio of products,
rather than just a single candidate at a time increases the probability of bringing a successful drug to market. BARDA has established these partnerships using the PAHPA-granted Other Transaction Authority (OTA) to create flexible, cost-sharing business partnerships between the government and industry. Portfolio-based funding reduces risk by allowing for the reallocation of resources across activities and among drug candidates if technical or business risks materialize. Since 2013, BARDA has successfully used its OTA twice to establish public-private partnerships. The establishment of the partnership with AstraZeneca fulfilled a requirement in the CARB National Action Plan to create at least one additional portfolio partnership with a pharmaceutical or biotechnology company by March 2016 to accelerate development of new antibacterial drugs, and several others are currently in negotiations.

BARDA works closely with other government funding agencies, specifically the National Institute of Allergy and Infectious Diseases (NIAID) within the National Institutes of Health, to provide support of product development from early stage discovery through to approval and procurement. While NIAID primarily supports early stage discovery of new drugs, vaccines, and diagnostics and preclinical product development up through Phase 1 clinical studies, programs normally become eligible for BARDA funding once an application to administer an investigational drug to humans is filed with FDA and the project is in Phase 1 development or later. BARDA works closely with our interagency partners, including NIAID and the programs in the Department of Defense, to identify and transition projects within their portfolios to BARDA where we can support the later stage clinical development of products from Phase 1 to approval.
In today’s marketplace, innovation often occurs in small biotechnology companies and in academic laboratories that lack the resources and expertise to move candidates along the development path from lead optimization to clinical development. Many promising early stage candidates, without the appropriate resources and support, will be unable to advance to late stage clinical development and approval. To overcome this problem, BARDA and NIAID are working together to establish and operationalize a new initiative we are calling the CARB Accelerator.

The CARB Accelerator will serve as an incubator for new products and explicitly seeks to reinvigorate the early stage antibiotic pipeline and repopulate the late stage clinical development pipeline with new and promising antibiotics. The CARB Accelerator will fund research and development activities to help progress candidate products from the proof-of-concept stage through pre-clinical development. BARDA will provide direct funding to launch the Accelerator in 2016, with a goal to support the program thereafter for five years, while NIAID will provide access to an array of product development support services. NIAID and BARDA will collaborate in managing the program and its investments through a joint oversight committee.

BARDA’s goal for the Accelerator is to stimulate the early stage development of new antibiotic candidate products and to progress products to the step of filing an FDA Investigational New Drug (IND) application, which is required before drugs can enter human clinical trials. After receiving the FDA’s authorization, products can then enter into the clinical development phase and thus become eligible for direct BARDA support. Successful products will emerge from the Accelerator as graduates with resources, networks and a robust product development strategy to support further clinical development.
In 2016, the Accelerator will accept proposals from innovators seeking support for the nonclinical development of their candidate products. BARDA looks forward to engaging the community of researchers and product developers through another novel public private partnership and re-inventing how government is able to partner with industry to address the urgent problem of antimicrobial resistance.

As new forms of antibiotic resistance continue to spread worldwide, the prospect of bacterial strains resistant to all available antibiotics can no longer be ignored; the continued development of new options for treating drug-resistant bacteria will be essential to preserving our ability to effectively combat infections. ASPR and its partners will continue to play a critical role in leading the charge against these threats, both present and future. We look forward to working with Congress to develop new antimicrobial therapies and non-traditional approaches to address the global challenge of antimicrobial resistance. Thank you again and I look forward to your questions.
Mr. MURPHY. Thank you, Doctor.
Now, Dr. Dixon, you are recognized for 5 minutes.

STATEMENT OF DENNIS M. DIXON

Mr. DIXON. Thank you, Mr. Chairman, Ranking Member DeGette—

Mr. MURPHY. Make sure the microphone is on and pulled close to you, OK?

Mr. DIXON. Mr. Chairman, Ranking Member DeGette, and members of the subcommittee, thank you for the opportunity to discuss antibiotic resistance, a serious and growing global health threat. I am Dr. Dennis Dixon, and I serve as chief of the Bacteriology and Mycology Branch in the National Institute of Allergy and Infectious Diseases.

The NIAID is the lead institute at the NIH for research on infectious diseases, including research on antibiotic resistance. NIAID’s longstanding research efforts in this area aim to understand the molecular basis of antibiotic resistance, as well as to develop specific and sensitive diagnostics, vaccines to prevent infections, and to partner with pharmaceutical industry companies in the development of novel and improved treatments.

The recent detection in the U.S. of bacteria resistant to colistin, an antibiotic of last resort, reminds us of the urgent challenge of drug resistance and the need to address its underlying causes. Fortunately, this particular bacterial strain was treatable by other antibiotics. However, the threat remains that this type of resistance could emerge in other bacteria resistant to most antibiotics making them untreatable with currently available drugs.

Through our research mission, NIAID plays a critical role in the administration’s national strategy and action plan on Combating Antibiotic-Resistant Bacteria or CARB. NIAID’s antibiotic resistance research portfolio includes basic research on how bacteria develop resistance and cause disease; translational research to develop diagnostics, therapeutics, and vaccines; and clinical research to evaluate antibacterial products and strategies.

Additional funding provided by Congress in fiscal year 2016 for CARB have been instrumental to our efforts. NIAID-supported basic research provides the foundational knowledge essential for the development of vaccines to prevent antibiotic-resistant infections and therapeutics to treat them.

As part of the CARB initiative, NIAID supports genome sequencing for a national database of antibiotic-resistant bacteria. This database, developed by NIH in collaboration with FDA and CDC, will provide a comprehensive resource for surveillance, epidemiology, and basic research into the mechanisms of antibiotic resistance.

NIAID also facilitates product development by providing non-monetary support to researchers, including genome sequences, access to clinical specimens, drug screening, and animal model testing. These resources provided much-needed support for the field and help to reduce the risk for product developers.

We also provide clinical trials capacity for evaluating new antibacterial products and strategies through our Antibacterial Resistance Leadership Group and other clinical trial networks for clinical
research on antibiotic resistance. We are currently in the process of expanding this infrastructure.

NIAID is also pursuing the development of point-of-care diagnostic tests critical to determining which drugs will be effective against given infections and recently awarded funding for research projects that develop rapid, sensitive, and specific diagnostic tools.

NIAID is working to discover better treatments to treat antibiotic-resistant infections by screening new compounds and optimizing the use of existing drugs. NIAID recently awarded funding for research projects to develop nontraditional therapeutics for bacterial infections and funds clinical studies testing new formulations, dosing regimens, or combination therapies of currently licensed drugs such as colistin.

In summary, NIAID is committed to a robust and comprehensive research effort to address antibiotic resistance and is fostering collaborations with partners in academia, industry, and the Federal Government. NIAID will continue support promising research to develop and test new antibiotics as well as methods to prevent the further spread of antibiotic resistance.

Thank you for bringing attention to this important topic. I'd be pleased to answer any questions.

[The prepared statement of Dennis M. Dixon follows:]
DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

The Role of the National Institute of Allergy and Infectious Diseases Research in Combating Antibiotic Resistance

Testimony before the
House Energy and Commerce Committee
Subcommittee on Oversight and Investigations

Dennis M. Dixon, Ph.D.
Chief, Bacteriology and Mycology Branch
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases

June 14, 2016
Mr. Chairman, Ranking Member DeGette, and members of the Committee, thank you for the opportunity to discuss antibiotic resistance, a serious and growing global health threat. The National Institute of Allergy and Infectious Diseases (NIAID) is the lead institute at the National Institutes of Health (NIH) for conducting and supporting research on infectious diseases, including research on antibiotic resistance.

NIAID has a dual mandate to balance a robust research portfolio in established infectious and immunologic diseases with the capacity to respond quickly to newly emerging and re-emerging infectious diseases. Infections resistant to currently available antibiotics are among the most urgent of these emerging threats.

Antibiotic resistance is a multifaceted problem, and multiple approaches are being undertaken to work toward a comprehensive solution. These include bolstering surveillance, diagnostic capacity, hospital infection control, and the prudent use of antibiotics in both humans and animals. Biomedical research also is essential to address the problem. NIAID’s longstanding research efforts in this area aim to understand the molecular basis of antibiotic resistance, to develop specific and sensitive diagnostics, to develop vaccines to prevent infections prone to resistance to antibiotics, and, importantly, to partner with the pharmaceutical industry to develop novel and improved interventions.

Antibiotic Resistance

The development and use of antibiotics to treat bacterial infections are among the greatest achievements of modern medicine. However, many of these drugs have become less effective over time as resistance to them has emerged and spread globally. The Centers for Disease Control and Prevention (CDC) estimates that each year in the United States, at least 2 million
people become infected with antibiotic-resistant bacteria and at least 23,000 people die as a result of these infections. CDC has identified the most serious antibiotic resistance threats in the United States including carbapenem-resistant Enterobacteriaceae (CRE), *Clostridium difficile*, *Neisseria gonorrhoeae*, and drug-resistant strains of *Staphylococcus aureus* such as methicillin-resistant *S. aureus* (MRSA).

The recent detection in the United States of bacteria resistant to colistin, an antibiotic of last resort, reminds us of the urgent challenge of drug resistance and the need to address its underlying causes. We were fortunate that this particular bacterial strain was treatable by other antibiotics; however, the threat remains that this type of resistance could emerge in other bacteria already resistant to most antibiotics, making them untreatable with currently available drugs.

**White House Initiative on Combating Antibiotic-Resistant Bacteria**

In 2014, the Administration announced a comprehensive set of new federal actions to combat the rise of antibiotic-resistant bacteria and protect public health, including the National Strategy and National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB). Key participants in the CARB effort include NIH; CDC; the Food and Drug Administration (FDA); the Office of the Assistant Secretary for Preparedness and Response (ASPR), including the Biomedical Advanced Research and Development Authority (BARDA); the United States Department of Agriculture; the Department of Defense; and others.

NIH plays a critical role in the CARB initiative through our research mission. Additional funding provided by Congress in fiscal year (FY) 2016 has been instrumental to our efforts, particularly in the areas of microbial genome sequencing, diagnostics and drug development, and clinical research, as described below.
In addition, NIAID is participating in the Administration’s National Action Plan for Combating Multidrug-Resistant Tuberculosis (MDR TB). The emergence of TB that is resistant to multiple antibiotics is a growing global concern. NIAID is leading research efforts to accelerate basic and applied research and development to combat MDR TB. This research complements other CARB efforts that target this increasingly prevalent drug-resistant infection.

**NIAID Research Addressing Antibiotic Resistance**

As outlined in the 2014 report entitled, “NIAID’s Antibacterial Research Program: Current Status and Future Directions,” NIAID supports a robust research portfolio that includes basic research on how bacteria develop resistance and cause disease; translational research to develop diagnostics, therapeutics, and vaccines; and clinical research to evaluate antibacterial products and strategies.

*Basic Research and Research Resources to Facilitate Product Development*

NIAID intramural scientists and extramural grantees are conducting basic research to understand microbial pathogenesis, including how bacteria colonize our bodies and evade immune defenses. NIAID-supported research also aims to discover mechanisms of antibiotic resistance. Basic research provides the foundational knowledge essential for the development of vaccines to prevent antibiotic-resistant infections and therapeutics to treat them. For example, NIAID researchers discovered that *S. aureus* produces peptide toxins critical for bacterial growth and pathogenesis in a mouse model, suggesting that the toxins themselves may be a target for development of new drugs for this important pathogen that may become resistant to methicillin or other drugs.
High-throughput genome sequencing efforts also are leading to a better understanding of bacterial pathogenesis and how antibiotic resistance develops. NIAID supports genome sequencing for a national genome sequence database of antibiotic-resistant bacteria as part of the CARB initiative. This database, being developed by NIH in collaboration with FDA and CDC, will provide a comprehensive resource for surveillance, epidemiology, and basic research into the mechanisms of antibiotic resistance. NIAID also funds a large-scale sequencing project to understand the genetics of drug resistance in TB. In addition, NIAID scientists and their colleagues have sequenced the complete genome of a drug-resistant strain of Klebsiella pneumoniae, which is a significant cause of hospital-acquired infections. This sequencing effort has revealed two different lineages of these bacteria with separate evolutionary histories, providing insight into the multiple pathways through which bacteria become resistant to antibiotics. Additionally, the NIAID-supported Bioinformatics Resource Centers have assembled the genome of the Escherichia coli containing the colistin resistance gene, mcr-1, isolated from the first patient in the United States (mentioned above), and has rapidly made it available to the research community for further study.

NIAID also provides a comprehensive set of research resources and services designed to reduce the risk to product developers and to help move concepts and candidate products along the research pipeline. These include genome sequencing, quality-controlled research reagents and clinical specimens, drug screening, and animal models to accelerate antibacterial product discovery.

In addition, NIAID is expanding its Antibiotic Resistance Leadership Group (ARLG) and other clinical trial networks, such as the Vaccine and Treatment Evaluation Units, for clinical research on antibiotic resistance. This expansion, facilitated by the CARB initiative and
associated funding, will increase the capacity to evaluate new antibacterial products and strategies and move needed countermeasures along the research and development pipeline.

**Diagnostics**

Rapid, point-of-care diagnostic tests can be important in determining precisely which drugs will be effective against a given infection, thereby reducing the inappropriate use of broad-spectrum antibiotics. Currently, broad-spectrum antibiotics that target a wide range of bacteria are often prescribed when a diagnosis is not available prior to starting treatment. The CARB initiative is incentivizing the development of rapid, point-of-care diagnostics to identify antibiotic-resistant bacteria and inform treatment of these infections. NIH and BARDA are collaborating to fund a $20 million diagnostic prize, and NIH held a public consultation and web-based forum to solicit comments on the technical criteria and performance characteristics of diagnostics to be considered for the prize. In addition, NIAID recently awarded more than $11 million in first-year funding for research projects supporting enhanced diagnostics to detect antibiotic-resistant bacteria. The grantees in this program will work to develop rapid, sensitive, and specific diagnostic tools that do not rely on the time-consuming process of growing the bacteria, which is how bacterial infections are often diagnosed currently.

NIAID also supports clinical studies through its ARLG to improve diagnosis of drug-resistant infections. The ARLG is developing a study to test procalcitonin, a biomarker that could help clinicians distinguish between bacterial and viral lower respiratory tract infections. Such a biomarker could help to reduce inappropriate use of antibiotics for viral infections, an important driver of the development of antibiotic resistance. Other ongoing ARLG studies are comparing the performance of existing diagnostics and validating new tools including platform diagnostics to rapidly identify antibiotic-resistant bacteria.
NIAID also has supported the development and validation of a test that can rapidly identify TB and simultaneously detect resistance to rifampicin, an antibiotic commonly used to treat TB. This test, and next-generation versions of the test, currently are being implemented in developing countries to diagnose TB, including drug-resistant TB.

**Therapeutics**

NIAID is screening new compounds and repurposing existing drugs to provide better options to treat antibiotic-resistant infections. In addition, many novel approaches are being explored, including monoclonal antibodies, bacteriophages, and strategies targeting the microbiome or the host immune system. NIAID recently awarded approximately $5 million in funding for 24 research projects seeking to develop non-traditional therapeutics for bacterial infections. These awards are investigating novel therapies such as bacteriophages, probiotics, and nanoparticles to treat or prevent infections. NIAID intramural researchers also are exploring a novel treatment for TB called host-directed immunotherapy. Rather than targeting the bacteria directly, this approach involves manipulating the body’s response to TB, using a regimen that includes zileuton, a clinically approved drug for asthma, to target components of the immune response. In addition, NIAID-supported scientists recently identified the drug teixobactin using an innovative iChip platform that allows researchers to screen natural products from bacteria that live in soil. This drug has a novel mechanism of action and has shown promise against several antibiotic-resistant microbes. Although teixobactin is still under development, potentially it could be a new tool to treat drug-resistant bacteria.

Optimizing the use of existing drugs also can help limit the development of antibiotic resistance. To this end, NIAID funds clinical studies testing new formulations, dosing regimens, or combination therapies of currently approved drugs such as colistin. NIAID-supported
researchers recently found evidence that two off-patent antibiotics, clindamycin and trimethoprim/sulfamethoxazole, work equally well against bacterial skin infections caused by MRSA, indicating that these infections can be treated successfully and inexpensively with either therapy. In addition, an ongoing NIAID-supported Phase IV clinical trial is comparing different combinations of existing antibiotics for treatment of gonorrhea, a disease for which drug resistance is a growing concern.

**Vaccines**

Developing vaccines to prevent infectious diseases can help prevent the inappropriate use of antibiotics and the development of antibiotic resistance. NIAID is developing vaccines to prevent infections for which treatment options are jeopardized by the emergence of drug resistance, notably staphylococcal infections and gonorrhea. Vaccines for viral infections such as influenza also may help reduce the use of antibiotics, which are often used inappropriately to treat viral infections, or appropriately used to treat bacterial infections that sometimes develop following viral infections. NIAID is working to develop vaccines for influenza, including several promising universal influenza vaccine candidates. A universal influenza vaccine could reduce or eliminate the need for annual seasonal influenza vaccines and provide long-lasting protection against multiple strains of influenza, including seasonal and pandemic influenza. Such a vaccine could lessen the burden of influenza and associated secondary bacterial infections, thereby reducing the need for antibiotics.

**Conclusion**

NIAID is committed to a robust and comprehensive research effort to address antibiotic resistance and is fostering collaborations with partners in academia, industry, and the federal
government. NIAID will continue to support promising research to develop and test new antibiotics as well as methods to help prevent the further spread of antibiotic resistance.
Mr. Murphy. I thank all the panel for their comments here. I am going to recognize myself for 5 minutes of questions.

On September 20 of 2000, then CDC director Dr. Jeffrey Koplan testified before Senate Appropriations Subcommittee on Labor, HHS, and Education on the emerging national and global problems of antimicrobial resistance and the response by CDC. And at that hearing the CDC unveiled its plan that targeted drug resistance. In particular, Dr. Koplan testified that a key part of this plan was developing a national campaign to improve physician prescribing practices and educate parents and patients about the proper use of antibiotics.

Dr. Bell, despite the CDC’s campaign as well as the efforts of others, the overprescribing of antibiotics still exists. So why did the overprescribing and overuse of antibiotics continue even with the CDC’s campaign?

Dr. Bell. Thank you very much, Mr. Chairman.

The campaign that I think you’re referring to is a campaign which is called Get Smart, and this is something that we’ve been working on for quite some time. But actually, we’ve had quite a bit of impact. Actually, we’ve been able to show decline. The Get Smart campaign was really focused on outpatient prescribing. And while we are very concerned about the continued overuse of antibiotics in outpatients, we’ve actually seen considerable improvements over the years and they’ve been able to show an impact of the Get Smart program.

Antibiotic overprescribing and stewardship is a complex issue, and we really need to attack it on many different fronts. The Get Smart and outpatient facilities is just one piece of the puzzle, and we’ve been really redoubling our efforts in the area of stewardship over the last few years releasing guidelines for stewardship programs and essential elements for hospitals and for long-term care facilities.

Mr. Murphy. Do you see trends changing, that it is getting through to physicians because——

Dr. Bell. Well, we now know that there are about 40 percent of hospitals in the United States that have all the elements of a stewardship program, and we’ve set a target of 100 percent of inpatient facilities by 2020. There are a lot of positive developments. I think——

Mr. Murphy. But go back to that number of the huge——

Dr. Bell. Yes.

Mr. Murphy [continuing]. Amount of prescriptions written every year——

Dr. Bell. Yes.

Mr. Murphy [continuing]. That shouldn’t be. So that doesn’t sound like it is working to me. I just want to know what else—we are here to help you.

Dr. Bell. Yes.

Mr. Murphy. We are all on the same team here. I know the White House Action Plan at Combating Antibiotic-Resistant Bacteria——

Dr. Bell. Yes.
Mr. MURPHY [continuing]. It is there. How is that going to be different? What do we see that is really going to get through to people this time?

Dr. BELL. Well, we really I think are just over the last few years really attacking this on lots of different fronts. As I said, the initial Get Smart program was really an educational campaign focused in one area, and now we have many different modalities. We've been collaborating very effectively also with CMS, with the American Hospital Association. CMS will be developing conditions of participation both for hospitals and long-term care that will require——

Mr. MURPHY. Will this also—excuse me.

Dr. BELL. Excuse me.

Mr. MURPHY. I have to jump in because we are short on time.

Dr. BELL. Oh, sorry.

Mr. MURPHY. Will this also include—and I ask the panelists. Will this also include information for patients?

Dr. BELL. Yes——

Mr. MURPHY. I mean, let's face it. People go to the doctor and say I want a prescription. He says, well, you have got a virus, it is not going to work; I want it anyways. And doctors now especially because they get rated on——

Dr. BELL. Yes.

Mr. MURPHY [continuing]. Were you treated satisfactorily and hospitals then get dinged. They don't get paid as much.

Dr. BELL. Yes.

Mr. MURPHY. And I have heard time and time again hospitals say, look, we are afraid of these ratings and so they will show up in Web sites, everything else. So what are we doing to combat that?

Dr. BELL. I appreciate your point. And we have been developing a lot of educational campaigns focused on patients. And I think you're right. Our objective would be for patients, when they go to the doctor and the doctor wants to prescribe an antibiotic, the patient says why do I need this antibiotic? Please explain that to me. And we do really need a sea change, and we're certainly working in lots of different ways to educate the patient. The patient really is pivotal in terms of solving this problem.

Mr. MURPHY. Dr. Woodcock, it is always good to see you. Why haven't we developed rapid diagnostic testing for bacterial infections yet? And can you tell us about some of the commercial and technical impediments here?

Dr. WOODCOCK. Well, it's just harder than it sounds. There are a few. We have strep test, and that's great, OK, so there's something where people can differentiate quickly and put people at ease perhaps that they don't have—don't need an antibiotic, an outpatient setting, right? The technology is advancing, as I said in my oral statement. The Center for Devices is seeing technologies come along in the development pipeline so we expect over the next several years we will see more rapid diagnostic tests in a variety of settings.

It's urgent that we try to find some that differentiate bacterial and virus infections. People are working on expression profiles that you can do a blood test and make that determination, and then you could reassure the patient you don't have a bacterial infection. And that would be very helpful.
Mr. Murphy. Thank you. I see I am out of time so I will recognize Ms. DeGette for 5 minutes.

Ms. DeGette. Thank you, Mr. Chairman.

As I said in my opening, I want to talk about how we can incentivize development of new antibiotics, and as we heard, earlier this year BARDA and NIAID collaborated to establish the Combating Antibiotic-Resistant Bacteria, or CARB, by a pharmaceutical accelerator. So, Dr. Hatchett, I am wondering if you can tell me very briefly why this program is important.

Dr. Hatchett. Well, thank you, Ms. DeGette for the question. As I said in my opening testimony, BARDA is very concerned. We do currently have a mature portfolio of antibiotics that are close to achieving licensure, but we are concerned that the upstream pipeline is very weak——

Ms. DeGette. Right.

Dr. Hatchett [continuing]. And that reflects the progressive disinvestment over several decades by biopharmaceutical firms not viewing antibiotics as providing sufficient return on investment.

The goal of the biopharmaceutical accelerator will be in collaboration with our partners at NIAID, and we’ve worked very closely with them to structure the accelerator to support that early development, bring resources and capabilities to early-stage innovators and help them move rapidly through the development process and advance those products hopefully to a point where they can transition to direct support for it.

Ms. DeGette. Thank you. And, Dr. Woodcock, I want to follow up on this because when you testified before this committee in 2014 about 21st Century Cures, you talked about this issue of lack of commercial incentives for drug developers and that being a reason why we don’t have new investigational drugs. Can you quickly update us on what the situation is since 2014 with this? Do we have some promising drugs in the pipeline? Are we fixing some of these commercial issues?

Dr. Woodcock. There are some promising drugs in the pipeline, but the pipeline is still very fragile. And what we need is not just a few superstars here. We need a full panoply of investment in the research, the basic science, the drug discovery and drug development that lasts, as Dr. Hatchett just said, over decades because we don’t just need a few antimicrobials, we need a whole continuum——


Dr. Woodcock [continuing]. Platform and range of them for a wide variety of diseases, and we’re just not seeing that, not all of the ones under development are going to succeed. And that’s true of all drug development.

Ms. DeGette. So Chairman Murphy and I got a letter yesterday from the Infectious Disease Society of America, and that organization said in their letter that the administration promised to release a report and recommendations on economic incentives for antibiotics, but the reported recommendations have not been released. I am wondering what the status of that report is and when it will be released.

Dr. Woodcock. I don’t know. It’s not under my purview, but we can get back to you.
Ms. DeGETTE. I wish you would, thanks, because maybe that can help illuminate—yes, Dr. Hatchett?

Dr. HATCHETT. I just want to mention that Secretary Burwell did ask the Presidential Advisory Committee on Combating Antibiotic-Resistant Bacteria to look explicitly at the issue of necessary economic incentives for the development of antibiotics. That letter was sent to the committee at the end of March, so they are actively undertaking that review.

Ms. DEGETTE. All right. Does anybody here know what this report is and when we are going to get it?

Dr. HATCHETT. The report was an internal report at the White House, and I don’t know the status of it. You’ll have to address the question to them.

Ms. DEGETTE. Dr. Dixon, can you talk to me about the clinical trials that are going on on strategies for using existing drugs more effectively?

Mr. DIXON. Absolutely. Thank you for the question. And it is important not only to develop new drugs but to optimize the ones we have left. And in fact, we have a clinical trial underway with colistin because we don’t know how long it will be before we run out of use of colistin. But knowing how to use it wisely——

Ms. DEGETTE. Right.

Mr. DIXON [continuing]. Will reduce the risk of emergence of resistance.

Ms. DeGETTE. OK.

Mr. DIXON. So we have looked at how the body metabolizes colistin—in other words, the pharmacokinetics—to maximize the presence of drug in the blood and maximize the activity of the drug and minimize the emergence of resistance. And so we have completed a study there that helped to inform better dosing of colistin——

Ms. DeGETTE. Right.

Mr. DIXON [continuing]. And we’re now looking at colistin alone versus colistin in combination with another drug for carbapenem-resistant Enterobacteriaceae, or CRE, and other resistant pathogens.

Ms. DeGETTE. Thank you.

Mr. DIXON. And so——

Ms. DeGETTE. Thank you very much. I want to ask Dr. Bell a quick question about why improved diagnostics are an important part of addressing the threat of antibiotics resistance.

Dr. BELL. Yes, thank you. As we’ve been talking, the issue of stewardship is so pivotal to addressing this whole issue of antibiotic resistance, and improved diagnostics, having the capability to be able to differentiate between a viral infection and a bacterial infection right there when the patient is sitting in front of you would be a really important tool that would help us in all of our stewardship efforts. So we really do hope that diagnostics that can at least perform that basic function will be something that’ll be available——

Ms. DeGETTE. Thank you.

Dr. BELL [continuing]. Relatively soon.

Ms. DeGETTE. Thank you so much, Mr. Chairman. I yield back.
Mr. McKinley [presiding]. Thank you. I recognize myself for 5 minutes.

This discussion reminds me a little bit of some of the environmental issues we have been dealing with over the last 5 years. The fact that we only represent such a small part, 5 percent of the population of the world, yet we consume so much of our energy, and what Gina McCarthy from the EPA there other day said that it makes no difference what we do; it is what happens around the world is what is really going to affect the environment, so notwithstanding all the issues that we have done in rules and regulations.

So my question goes back to my opening statement, was when with 95 percent of the rest of the world perhaps overprescribing antibiotics and we don’t know what is happening in some other nations around the world. We know 20 nations at least and Mexico are over-the-counter for antibiotics. This global issue, what should we be doing? We can solve it here, but if indeed the patients, people are coming in that have drug resistance to our antibiotics, what do we do? So if the four of you could just give me a sense. This fight is a global fight, not a United States. Please, Dr. Bell.

Dr. Bell. Thank you. Yes, you’re absolutely right. This is definitely a global fight. These microbes move around the world, and we have to look at this from a global perspective.

So we are working in a number of different areas. So, first of all, we do have a number of really excellent collaborations with the Europeans and the Transatlantic Task Force for Antimicrobial Resistance, which allows us to share information very quickly, develop common standards, and also pool our resources to help other countries around the world. That’s a very effective collaboration.

The World Health Organization is actually getting serious about antibiotic resistance. The World Health Assembly has passed several resolutions with all nations basically committing to do something about antibiotic use. So we have to do everything we can to support them——

Mr. McKinley. But even with our education——

Dr. Bell [continuing]. And we are——

Mr. McKinley [continuing]. We are still at——

Dr. Bell. That’s right. It’s a hard problem. And we haven’t solved it here——

Mr. McKinley [continuing]. Forty percent, so even with our education level here——

Dr. Bell. That’s right. It’s a hard problem.

Mr. McKinley [continuing]. I am troubled about other areas, emerging nations——

Dr. Bell. Yes.

Mr. McKinley [continuing]. What is happening. So please continue.

Dr. Bell. I think——

Mr. McKinley. I am not sure I am buying into all the educational part of it. I am trying to figure out what the other solution is.

Dr. Bell. Yes. No, I think there are many parts of this. It can’t just be education, you’re absolutely right. There have to be national policies and there has to be national legislation that supports this
sort of antibiotic stewardship around the world. And as I say, I think that there is a fair amount of interest in that.

We've been working also a lot on improving detection so that at least we know what's emerging where, and this is something that——

Mr. McKinley. Let——

Dr. Bell. Go ahead. I'm sorry.

Mr. McKinley. Let's go to that point.

Dr. Bell. Yes.

Mr. McKinley. Are there nations that are more prone to have problems that we need to deal with——

Dr. Bell. Well——

Mr. McKinley [continuing]. Around the world? Because we are not all equal so——

Dr. Bell. No, we're not all equal, and there certainly are some countries that do have already a significant problem with, for example, bacteria that are resistant to all antibiotics. Colistin that we've been talking a lot about here is actually used quite a bit more to treat human infections in other parts of the world, in India, for example, because there are unfortunately a large number of patients that show up in intensive care units, for example, that are infected with bacteria that are resistant to all other antibiotics. So this is a larger problem in some other parts of the world. There are some hot spots. And this issue of detection and focusing on the hot spots and knowing where the hot spots are is something that we've been working on.

The Global Health Security Initiative includes antibiotic resistance as one of the areas that the countries have agreed to focus on so——

Mr. McKinley. Should we be spending more of our monies overseas to try to work those problems out over there?

Dr. Bell. Well, I think that it would be not wise for us not to focus on our local problem here. If we don't know what's going on here, we're not going to be able to protect Americans. We have to be doing both because we have to be both strengthening our ability to prevent and detect and respond in the United States while at the same time supporting global efforts.

Mr. McKinley. OK. So two quick questions. One, Colistin, is that a reasonably marketable, affordable drug or is this something——

Dr. Bell. No, colistin is a very old antibiotic. It's been around for a long time. As a physician, I hate to prescribe colistin to patients. And actually in any country doctors really don't want to use it. It has a lot of potential side effects. It has kidney toxicity, it has brain toxicity. So it really is a last-resort antibiotic.

Mr. McKinley. I am afraid my time is expired, but thank you very much for your responses.

If I could, next line of questioning from Mr. Pallone, 5 minutes.

Mr. Pallone. Thank you, Mr. Chairman.

I wanted to ask each of you a question about investment in fighting antibiotic resistance, so I am going to go through quickly so I can get to each of you.

In the last few years, we have seen increased investment in this fight. The President released the National Action Plan for Com-
bating Antibiotic-Resistant Bacteria in March of last year with ambitious goals for many Federal departments and agencies. And I am encouraged by the over $830 million we directed toward this effort in fiscal year 2016. And the President, as you know, has requested $1.1 billion for fiscal year 2017 for antibiotic resistance.

So let me start with Dr. Bell. In your prepared testimony, you noted that CDC has received $160 million in fiscal year 2016 to implement the National Action Plan noting that, “These resources are transforming how our nation tackles and slows antibiotic resistance comprehensively, efficiently, and systematically.”

So just tell me, how will the increased investment requested for the next fiscal year build on this capacity, and why is sustained investment critically important to our success in combating antibiotic resistance?

Dr. Bell. Thank you. So antibiotic resistance is a problem in communities, so a lot of our funding in 2016, for which we are very grateful to Congress, is being used to fund states and large cities to build their capacity to detect and to respond and to prevent. And so the additional funding in 2017 will go towards being able to go even further in that regard. So we’ll be able to fund more states to have the kind of antibiotic-resistant prevention programs. We’ll be able to strengthen our laboratory networks so that we can look for more types of antibiotic-resistant organisms. And in general, we’ll be able to take the kind of investments that we’re making in 2016 to more states and to a higher level.

Mr. Pallone. Thank you. Dr. Dixon, in your testimony you noted that the additional funding for fiscal year 2016 has been instrumental to NIH efforts. Again, why is sustained investment in fighting antibiotic resistance critical to your agency?

Mr. Dixon. Thank you for the question. We appreciate the additional funding, and we’re applying that to such key resources as the National Sequence Database that will inform the sequences and tracking genes like the MCR–1 and others; and diagnosis and going particularly after the problem of diagnostics, which could certainly help to reduce the overprescribing whether or not you have a bacterial infection or a viral infection; advancing basic translational and clinical research overall, fundamentally addresses the problems that can help to identify new candidate drugs, new candidate vaccines, and new candidate diagnostics. And to close up, just to say that we are contributing with BARDA the $20 million diagnostics prize to try and draw key manufacturers into the space.

Mr. Pallone. Well, thank you. So, Dr. Hatchett, you work with industry to bring new antibiotics to market. How is sustained investment important to your work, and what message does that send to your private partners? The same question.

Dr. Hatchett. Yes, I was going to say. Let me address the question of the value of the funding—

Mr. Pallone. Sure. Sure.

Dr. Hatchett [continuing]. For BARDA. As I mentioned, we established our Broad Spectrum Antimicrobials program in 2010. We did that with funding that was provided by Congress for biodefense purposes. And so we were very diligent in making sure that every antibiotic that we were developing had a biodefense application. For better or worse, what that meant was that we had to develop
broad spectrum antimicrobials, which are part of the problem that has contributed to the spread of resistance because of the overuse of broad spectrum antimicrobials.

The funding that Congress provided in 2016 is specifically dedicated to the problem of antimicrobial resistance, and it allows us to think in much more nuanced ways about how we can build up an armamentarium to treat patients who have antibiotic-resistant bacteria so we can make investments in vaccines, we can make investments in monoclonal antibodies and alternative therapies. So strategically, it's very important.

In 2016, we are making a number of investments. You've heard about the CARB accelerator. That's a major investment this year. You've heard about the diagnostics prize. We're also going to be expanding our portfolio partnership this year. All of those efforts are going to take years to mature and to convince our industry partners to enter into partnerships with us in an area that they have traditionally viewed as not providing an adequate return on investment. They have to see that sustained commitment of funding over many, many years and recognize that the government is a reliable partner.

Mr. Pallone. Thank you. I am out of time for you, Dr. Woodcock. Sorry. Thank you, Mr. Chairman.

Mr. McKinley. Thank you. And next, Dr. Burgess from Texas for 5 minutes.

Mr. Burgess. Thank you, Mr. Chairman.

Probably of all the members on this committee I have prescribed the most doses of antibiotics. Dr. Bucshon, who was here, is actually significantly younger than I am, so I think I probably have seniority on his as far as the doses of antibiotics.

And it is worth considering just a couple of historic notes as we talk about this. 1929, Sir Alexander Fleming noticed the zone of inhibition around a mole that had grown on his agar plate, and that led to the development of what we now know as penicillin. But it was really 15 years later when the Pfizer Corporation figured out how to manufacture this on a large scale so literally making this wonder drug, which previously was kind of a parlor trick, making it available to the masses and having it available to treat our soldiers on the days that they stormed the beaches at Normandy, thus resulting in significantly lower loss of life and limb from those soldiers who took that beach on that heroic day.

My grandfather practiced obstetrics. He was an academic physician. He unfortunately died in 1940 so he practiced obstetrics in the pre-antibiotic days, and I always kind of look at that with kind of wonder and amazement. Here was an individual that chose a profession before the development of good anesthesia, blood banks, and most of all, antibiotics because anyone who has practiced obstetrics knows that without the ability to prescribe good antibiotics and antibiotics that work well, our ability to fix problems has become severely limited. So we want the antibiotics that we have available to continue to work, and we want them to work well.

The JAMA article that was referenced is of interest, and I thank the staff for pulling it for me so quickly. And just glancing through it, it seems like pharyngitis, otitis media, and sinusitis are the illnesses or the diagnoses that sort of achieve the lion's share of the
antibiotic prescriptions. And easy to be critical of the doctors and practitioners who are prescribing those antibiotics, but let us not forget that 130 years before penicillin was discovered, the father of our country succumbed to an illness that was treatable by penicillin, a complication of pharyngitis, tonsillitis, that led to a peritonsillar abscess and ultimately took his life. So bacterial diseases are interwoven within our country’s history for the last, what, 85 years, have become part of the story of American medicine.

Dr. Dixon, let me just ask you because this is such an unusual situation with this woman that had the infection. She had an Enterobacter infection? Is that correct? Do I understand the story correctly?

Mr. Dixon. I think you do. It might be better of Dr. Bell, who followed that case and did the case study, could talk about the clinical workup of that individual.

Mr. Burgess. So how in the world did you find this plasmid or this gene that was so unusual? Was there something about this patient’s presentation that said we better look for this rare gene?

Dr. Bell. No. Actually, this story really begins with—it’s sort of a case study in how beefing up surveillance can really make a big difference in terms of prevention and response. So since we first heard about this MCR–1 identification in China, all of us in the Federal partners, including the Department of Defense, have been looking for evidence of this gene. And so the Department of Defense has a surveillance system where patients with bacterial infections or isolates within their system that have certain characteristics—in this case, show resistance to some of the extended spectrum beta lactamases—are shuttled eventually to the Walter Reed where they fully characterize these unusual isolates. And it was in the context of that that this was actually—that this was identified.

Mr. Burgess. But there was nothing in the patient’s clinical course or her diagnostic presentation that said, oh, boy, we better look for this one needle in the haystack?

Dr. Bell. No. That’s right, there wasn’t. And actually, just to clarify that this bacteria actually is not a pan-resistant bacteria. So the bacteria that infected this patient is actually treatable by some antibiotics, and the patient herself is actually fine. Indeed, in our field investigation and follow-up we’ve been able to verify that she no longer has that bacteria in her urine.

Mr. Burgess. Well, that is good news, but I guess the other question that comes up is how do you know this hasn’t occurred on other occasions—

Dr. Bell. Absolutely.

Mr. Burgess [continuing]. In all of the vast number—

Dr. Bell. We—

Mr. Burgess [continuing]. Of specimens—

Dr. Bell. Right.

Mr. Burgess [continuing]. That aren’t subject to that type of scrutiny?

Dr. Bell. We do not know, and I think that’s to the point about what are we doing with the investments that are available to us because of Congress’ appropriation is that we are going to be—and this is one of the things I think we’ve been concerned about for a
long time, that, for example, the CDC being the only lab in the country that can actually look for some of these unusual types of resistance, that's not a good state of affairs. And with the additional investments, we're going to be able to have a much more robust system for systematically looking for these and for looking for other and new, more emerging forms of resistance. In terms of responding to this finding, that's really the first thing that we want to do. We need to figure out how big a problem this is——

Mr. Burgess. Yes.

Dr. Bell [continuing]. As you say, Congressman.

Mr. Burgess. Right. Thank you, Mr. Chairman. I will yield back. Maybe we will have time for a second round.

Mr. McKinley. Our next is Congressman Green from Texas for 5 minutes.

Mr. Green. Thank you, Mr. Chairman.

Antibiotic resistance is a significant public health challenge, and we need think creatively to address it. And I want to hear from our witnesses today about the regulatory and scientific challenge in developing new antibiotics, especially focused on what we can do to tackle them.

Dr. Hatchett, what are some of the challenges facing manufacturers in the antibiotics market?

Dr. Hatchett. Thank you for the question, Congressman Green. Certainly there are scientific challenges, and I may turn to my colleague Dr. Dixon to let him address the scientific challenges. I'm just a dumb oncologist so this is not my field, but I do understand the medicinal chemistry particularly for gram-negative bacteria, which are some of the bacteria that we are most concerned about is particularly challenging.

From where I'm sitting, I think the biggest challenges relate to the economic incentives in fact to convince companies to make the long-term investment to do the development. But that wasn't your question.

Mr. Green. But what I was trying to get at is that we have both scientific challenges but we also have financial challenges because vaccines are not the next miracle drug. In some cases it could be.

But, Dr. Woodcock, would you like to add anything on the issue between——

Dr. Woodcock. Well, I do believe that——

Mr. Green [continuing]. The economics and the scientific——

Dr. Woodcock. I've talked to some of the large pharmaceutical companies. In the past they have run very broad scientific discovery programs and discovery means they're looking for antimicrobials, OK, they're trying to find candidates. And these programs have failed. So down at the science level, this is hard, and I think this is where NIAID's investment in the science of determining what are the bacteria like and how do they generate resistance and what is very important to advance that science because this is a hard area to develop drugs in.

Mr. Green. Thank you. Dr. Hatchett, these next questions are for you. Is BARDA exploring any new ways to incentivize development of these new antibiotics and other therapeutics?

Dr. Hatchett. Yes, sir, we are. I mentioned our use of our other transaction authority that Congress granted to us in the Pandemic
and All-Hazards Preparedness Act. And that allows us to work with companies, particularly large companies that have multiple products in their pipeline. And so we can invest in their entire pipeline as opposed to making a specific investment in a single product.

That approach has attracted a great deal of attention from large pharmaceutical partners. We have two of those portfolio partnerships now, one with GSK, one with AstraZeneca, a number of others are actually in negotiations. The companies find it very attractive because it allows them to keep a focus on the development of anti-infectives in a way that makes economic sense to them. So that's very important.

There is an emerging consensus about economic incentives, that it's going to require both a combination of traditional what we call push incentives or investments in R&D, R&D contracts, as well as pull incentives, the market-entry incentives. If you make it to market, there's a guaranteed market, a guaranteed return on investment, potentially a prize.

Mr. GREEN. OK. That brings us to the GAIN Act from last Congress and the ADAPT Act in this Congress, both individually but also as part of the 21st Century Cures. Envision a scenario where more adaptive clinical trials may be used to help drug developers seeking to create the next antibiotic drug effective against drug-resistant bacteria. Dr. Woodcock, can you tell me your thoughts on how the pathway laid out in ADAPT might benefit drug companies in the pursuit of the new novel antibiotics?

Dr. WOODCOCK. Certainly. Well, after a candidate is discovered and it's for a resistant organism, then you have another scientific problem of how do you find these people who are infected who are maybe scattered around and then test the drug in them when they're critically ill and they need to be treated right away. And so doing these clinical trials, even small clinical programs are extremely challenging. And of course we want the drug to be used in the most resistant organisms, so we want it to be tested there to see if it works. But those are hard to find. And so you have this big problem.

And we are interested in having a limited development program where you'd really have a great deal more uncertainty, but you wouldn't use the drug for sinusitis and otitis media and so forth. This would be signaled that there was only a limited amount of information, but the drug could be used in these desperate situations. And that pathway, we think, would be a reasonable pathway to make the drug available but with a stewardship signal.

Mr. GREEN. OK. Thank you, Mr. Chairman. I know I am out of time, but, Dr. Burgess, I have sinus troubles and every once in a while I get an infection. I will not call you for a prescription.

Mr. BURGESS. Flonase, bubba.

Mr. GREEN. I already take everything else.

Mr. MCKINLEY. All right. The chair recognizes Mr. Collins from New York for 5 minutes.

Mr. COLLINS. Thank you, Mr. Chairman. I want to thank the witnesses as well. It has always been a concern to many of us, but maybe to answer a question that I know goes through a lot of families when our kids say I have got an infection, I need an antibiotic.
And many moms and dads say, well, no, if you take these antibiotics, you will become antibiotic resistant, and some day when you are older and you really need one, it is not going to work. Contrasted to what we are talking about today is it is not a person who becomes antibiotic resistant, which is kind of this old wives’ tale versus there are bugs that are figuring out a way to become antibiotic resistant. And a person getting one of those bugs, even if they have never taken an antibiotic in their life, has the same risk. Would that be a fair——

Dr. WOODCOCK. Yes.

Mr. COLLINS [continuing]. Summary?

Dr. WOODCOCK. Yes, Congressman. If I could use that——

Mr. COLLINS. Yes.

Dr. WOODCOCK [continuing]. Myself, it would be helpful. That’s—no, that’s absolutely right. And that’s part of the point about how antibiotic resistance is really a problem for everybody because it’s not an individual that develops resistance. It’s the bacteria. And these bacteria are constantly replicating and they share genetic material and they spread around the community. So this is exactly—your explanation is exactly correct. And I’ve often thought we need a better term than resistance because people think that applies to them, and actually——

Mr. COLLINS. As a person.

Dr. WOODCOCK [continuing]. It doesn’t. It applies to the microbe itself. So again, we’ve oftentimes thought, you know, perhaps we need a better way to explain this to break that old idea——

Mr. COLLINS. Well, sure. I mean——

Dr. WOODCOCK [continuing]. That it’s a person.

Mr. COLLINS [continuing]. You can actually have in a family someone who should take an antibiotic, but because of this misconception——

Dr. WOODCOCK. Yes.

Mr. COLLINS [continuing]. The parents are saying, no, no, no, no.

Dr. WOODCOCK. Yes.

Mr. COLLINS. We are going to fight this for a few days, fight this for a week——

Dr. WOODCOCK. Yes.

Mr. COLLINS [continuing]. Because we don’t want you to become antibiotic resistant.

Dr. WOODCOCK. Yes, you’re absolutely right. I mean, antibiotics, as we’ve heard are—you know, they’re a treasure and they’re incredibly important and we need to—when we talk about stewardship, we don’t mean don’t use antibiotics. We mean use the right antibiotic at the right dose for the right duration for the right indication. And it is a very important part of our message.

Mr. COLLINS. Well, I think that is. That is why these hearings can be important.

Now, I have got a question for Dr. Dixon. I understand at Washington State University—and maybe this will translate to Dr. Woodcock—but I understand they have like an e-bandaide, an electromagnetic thing that they are going to put on someone, they pass the electric current through, they have now determined that is producing hydrogen peroxide. And if they control this, they have gotten some interesting results as a way to treat bacterial infections
and wounds without antibiotics. Are you familiar with some of that, and do you have a comment on—I know it sounds a little sci-fi-ish, but it actually seems to have some possibilities.

Mr. Dixon. I understand the question. I'm not familiar with that particular example. It is entirely consistent, though, with our approach of looking at things other than traditional drugs, so we're looking at exploiting the host immunity a better way. We're exploiting things like bacteriophage. We're exploring things like microbiota using microbial ecology to outcompete and prevent infections and other alternative approaches that don't provoke the emergence of resistance.

Mr. Collins. Yes, I think it makes a lot of sense sometimes to——

Mr. Dixon. Absolutely.

Mr. Collins [continuing]. Actually think out of the box, and if you had a chance, you should maybe look into this. It was Washington State University last November, about 6 months ago. The results sounded very encouraging because instead of by guess and by golly, they finally figured out why electric currents sometimes work and sometimes didn't, and it was controlling the process and it all came down to the hydrogen peroxide at a level of consistency that would say, on Shark Tank, this one might get funded. Who knows?

Mr. Dixon. Absolutely. A lot of exciting things going on out there.

Mr. Collins. So question for you, Dr. Woodcock. Let's say something like this happens. Now, this is an electrical therapeutic if you will. It is not a "drug." What role would the FDA have, and would you have to run clinical trials like it would be a drug or is there something else when it is almost like a device or something instead of a drug?

Dr. Woodcock. Well, there has to be a determination first whether it's a drug or device, and we have a process that's been set up by Congress, an office that sorts that out and what has to be done to study it. It depends on whether it's a device, a medical device or a drug, and those are appropriate to the two different kinds of——

Mr. Collins. Being one or the other, it would still have to go through your agency for approval——

Dr. Woodcock. Yes.

Mr. Collins [continuing]. Final signoff if you will.

Dr. Woodcock. These type of therapeutics, whether they're devices or drugs, are regulated by the FDA.

Mr. Collins. OK. And no idea what this one would be, but I think all of us are encouraged there may be in this high-tech world we live in now something other than antibiotics. At the same time, we have got to keep searching, and it is kind of an all-of-the-above search if you will. Thank you for your testimony. My time is expired and I yield back, Mr. Chairman.

Mr. McKinley. Thank you. And I now recognize for the next round of questions Ms. Castor from Florida for 5 minutes.

Ms. Castor. Thank you, Mr. Chairman. Thank you all for your expert testimony today.
I want to return to the discussion of how we tackle this internationally, as Mr. McKinley focused on, because no single country like the U.S. can do this alone. We are so interconnected now. People travel. You said microbes travel, animals travel, food travels. In July of 2014, the U.K. commissioned a study on the global problem of antimicrobial resistance. The study concluded that we must be concerned about drug resistance globally if we expect to be safe at home. An important theme discussed in the report is that infectious diseases profoundly affect poorer countries due to unsanitary living conditions. Unsanitary conditions, the report says, "act as a catalyst of rapid person-to-person spread, which can lead to an increase in the use and overuse of antibiotics."

Dr. Bell, what effect do poor living conditions and access to clean food and water have on the spread of infectious diseases, and how can poor sanitation contribute to the overuse of antibiotics?

Dr. Bell. Yes, thank you. This is unfortunately very much the case that—and you could imagine how, if you think about our prevention strategies in terms of infection control and in terms of hygiene how countries where people really just don't have the option of this sort of hygiene that we can—the level that we can establish here in the United States, but this does contribute to spread. And we see this in many countries around the world.

I think one of the things that we've learned is that I think it makes sense to sort of break some of this down in order to approach it. And infection control in hospitals, for example, is one component that we've really been working now with a lot of countries to at least improve infection control in facilities. If we see that, a lot of the most resistant bacteria are in facilities. We've been working with a number of countries in India, in West Africa—you heard with Ebola that's not about antibiotic resistance, but we certainly saw what the importance of infection control was.

Ms. Castor. So when poor countries address problems such as sanitation, access to clean water and infections in their medical facilities—this is basic—that helps reduce antibiotic resistance. And what more can be done then? We have so many fantastic nonprofit organizations, academics, churches, the developed world. What else can that group be doing to reduce the spread of infection?

Dr. Bell. Yes, you're absolutely right. And actually, I'll go back again to Ebola while that isn't a resistant organism. In our work in West Africa to improve infection control, we used many non-governmental organizations, church groups, and other sorts of non-governmental groups as trainers, as extenders, and as groups that can stay in the area and help the ministries of health and the hospitals with infection control.

Ms. Castor. So some experts have said and the U.K. report said and I think Mr. McKinley had said what needs to be done. They emphasized kind of some global organizing, collaborative or campaign. How could we go about such an effort?

Dr. Bell. The World Health Organization actually is in the process of organizing such a campaign, and while we all need to participate in that and provide some leadership.

Ms. Castor. So that would include tackling the over-the-counter prescriptions of antibiotics? The U.K. study reported that in parts of Southern and Eastern Europe, 20 to 30 percent of antibiotics are
consumed without a prescription, and in parts of Africa, the figure rises to 100?

Dr. BELL. Yes. That's definitely part of what we have to tackle.

Ms. CASTOR. OK. And then, Dr. Woodcock, Internet sales of antibiotics is a huge problem that this committee has documented extensively. You have testified before this committee multiple times on the use of Internet drugs. What role does FDA believe that Internet drug sales have on drug resistance across the globe?

Dr. WOODCOCK. I don't think we know in the United States. We intercept some packages and so forth. Most of the ones that we intercept are not antimicrobials. But certainly that could play a role. But I think that's something that's very difficult to get your hands around because, again, it's an international problem. Some of these are counterfeit, and that often plays a big role, especially in places like Africa or potentially even here because they don't have the right amount in there but they may have a low amount of antimicrobial in them, which then promotes the generation of resistance. So the free flow of antimicrobials, whether from over-the-counter use or through the Internet, is a potentially continuing large problem and very difficult to manage.

Ms. CASTOR. Thank you very much.

Mr. BURGESS [presiding]. The chair thanks the gentlelady. The gentlelady yields back. The chair recognizes the gentlelady from Tennessee 5 minutes for questions.

Mrs. BLACKBURN. Thank you, Mr. Chairman.

And I appreciate the patience you all have had with us this morning as we are running up and down to committees, hearings going on at the same time. So we have been in and out and you have been patient.

Dr. Hatchett, I want to come to you. Going back into February BARDA established the accelerator to support and research and development—and of course as we have worked on 21st Century Cures, we have been so interested in that, and then looking at the candidates that you were going to accelerate through this program with the drugs and vaccines and diagnostics and move that into development. And for us then moving it on to commercialization and into the mainstream.

I would like it if you could take just a minute and talk a little bit about the specific candidates that you all have put in that, about some of the vaccines or the microbials, some of the alternative therapies that you are reviewing in that program.

Dr. HATCHETT. Yes, ma'am. Thank you for the question. Just to be clear, the accelerator has not been established yet. We put out the solicitation earlier this year, and we have received the proposals. We had a good response, and we actually are in the process of negotiating with the lead candidates right now. So we haven't——

Mrs. BLACKBURN. OK.

Dr. HATCHETT [continuing]. Made the award——

Mrs. BLACKBURN. When you say a good response, quantify that for me a little bit.

Dr. HATCHETT. We had a pre-proposal conference where we had a—I don't remember the specific number, and I'm under oath, but I can get it for you.
Mrs. BLACKBURN. That would be great.

Dr. HATCHETT. But we ended up with five proposals, which really aggregated—actually some of the people that came to the pre-proposal conference met each other and then decided to partner, which made the proposals stronger. So I believe we had five proposals. And one of the requirements of—I don’t think it was a requirement, but we requested it. It was that people making a proposal to us could leverage the U.S. Government funding by gaining access to additional funding either from other funders or other venture capital entities, for example, that was going to be viewed as a positive. And fortunately, we had tremendous success with that, so we think when we make the final award, actually our investment, which this year could be as much as $30 million——

Mrs. BLACKBURN. OK.

Dr. HATCHETT [continuing]. May serve as a catalyst for additional investment coming in from other funders, even other countries that may be interested because of the way we’ve structured it. The—Ms. Castor mentioned the July 2014 U.K. study that was put together and led by Jim O’Neill, who was the former CEO of Goldman Sachs, and one of the recommendations of that study was to create a global innovation fund for antibiotic development. And actually, the United Kingdom and China have already made contributions of about $50 million to such a fund.

We think the accelerator will certainly bring in that level of funding. We are committed to providing up to $250 million for the accelerator over the next 5 years, and that could be a major, major catalyst for international collaboration to support this early-stage development.

Mrs. BLACKBURN. OK. And what is your expectation once you are able to populate the accelerator basically? Then how long do you think it will be before we begin to see next-generation products that are ready to go to the marketplace?

Dr. HATCHETT. So the accelerator, as I mentioned earlier, we are partnering very closely with our colleagues at NIAID. And NIAID has a full suite of what we call product development support services that can help innovators in the early stage accelerate their development. Our funding will allow those innovators to accelerate their timelines for bringing these products forward, and so we may be able to shorten the timelines. If those innovators were left to their own devices and left to the vagaries of the capital markets, it might take them many years to bring those products to the point that they would be ready for advanced development. The things that are in the accelerator are not going to pop out of the accelerator right into the marketplace. They’re going to be brought to the stage of clinical development——

Mrs. BLACKBURN. Right. We——

Dr. HATCHETT [continuing]. Which could take several years.

Mrs. BLACKBURN. We understand that, but we——

Dr. HATCHETT. Right.

Mrs. BLACKBURN. When we look at some of these drugs that are taking 10 years, 12 years to get through the process, and you look at the entire compendium and you look at what goes on with them, the innovators working with the FDA, our hope is that we are going to see your process work and help to push this to the market-
place sooner, that there will be some efficiencies. We know you have got some challenges, but we are hopeful there will be some efficiencies in moving it forward.

Dr. HATCHETT. Ours too, ma’am. The perhaps relevant example—its slightly different scale of urgency—but when we have had to respond to events like the Ebola epidemic——

Mrs. BLACKBURN. Yes.

Dr. HATCHETT [continuing]. Or to the pandemic in 2009, we were able to push things forward with incredible velocity and so shorten normal development time frames. It might be 5, 7, 10 years down to even, you know, 9 months, a year, 2 years——

Mrs. BLACKBURN. OK.

Dr. HATCHETT. I’m not promising——

Mrs. BLACKBURN. That is helpful.

Dr. HATCHETT [continuing]. That we can do that with the accelerator——

Mrs. BLACKBURN. Right.

Dr. HATCHETT [continuing]. But that’s the idea.

Mrs. BLACKBURN. That is helpful. That is what we want to hear. Thank you. I yield back.

Mr. BURGESS. The gentlelady yields back. The chair thanks the gentlelady.

And the chair recognizes the gentleman from New York, Mr. Tonko, for 5 minutes, please.

Mr. TONKO. Thank you, Mr. Chair.

My good friend and colleague, Representative Louise Slaughter, to my knowledge the only microbiologist in Congress, has been raising alarm bells for quite some time about the excessive use of antibiotics in our farm animals and feedstock.

I know that the FDA has shared similar concerns about antibiotic use and resistance in farm animals. In fact, FDA’s Center for Veterinary Medicine has developed a multipronged effort to limit or reverse resistance arising from the use of antibiotics in food-producing animals.

Dr. Woodcock, I understand that FDA’s efforts to control antibiotic use in farm animals are not entirely in your wheelhouse given where you sit in the agency. However, can you walk us through what FDA is doing to address the nexus between antibiotic resistance and the overuse of antibiotics at the farm?

Dr. WOODCOCK. Yes. As I said in my oral testimony, the Center for Veterinary medicine has sought commitments from the manufacturers of animal drugs that have important medical uses, and they have all committed to submit supplements that would basically change these drugs to prescription only. And that means they would not be used for growth promotion purposes, and they would need to be prescribed by a veterinarian. The Center for Veterinary Medicine expects this to occur at the end of the year, the supplement submission. And so soon after that the changeover could be accomplished is my understanding.

Mr. TONKO. And with that in mind, in any way are we making progress in overuse of antibiotics in our food supplies?

Dr. WOODCOCK. That I can’t answer but we could get back to you on that.
Mr. Tonko. Thank you. I would appreciate that. And, Dr. Woodcock, how are we tracking how much and what kinds of antibiotics food producers are using, and who is in charge of that effort? And just what is being done?

Dr. Woodcock. Well, in speaking to the Center for Veterinary medicine, I understand that tracking down to that level is difficult right now. We don’t have a billing system similar to what we have for human drugs where we understand what prescriptions are issued for what animals and so forth. So my understanding is that that’s a difficult set of information to find out.

Mr. Tonko. And I understand that one concern of regulators is that antibiotics have been used extensively for feed production purposes and not only for therapeutic purposes. So can you describe how antibiotics have been misused in that regard?

Dr. Woodcock. Well, there’s been a long tradition as I understand—I’m not a veterinarian—but I understand there’s been a long tradition of using certain amounts of antimicrobials preventively or in food that—in feed for the animals that results in some growth acceleration of the animals. And it’s not treating an infection or anything like that. It’s simply to put it in the feed and then the growth accelerates. And of course they’re being produced as food animals, and so that is an economic benefit. That type of use is what’s been addressed by the step that the Center for Veterinary Medicine is taking.

Mr. Tonko. And what are FDA and USDA planning to do to address that aspect of the problem?

Dr. Woodcock. Well, we expect the manufacturers will honor their commitments. They will submit supplements, and these will be changed. They cannot be used for growth-promoting purposes, these medically important antibiotics.

Mr. Tonko. Are there any other efforts that can be made by FDA to control the use of antibiotics in our food supplies?

Dr. Woodcock. Well, I think there’s always more that can be done, and I also believe that the norm system is very important and probably needs to continue to be strengthened. I think the value of surveillance just can’t be overestimated because we need to know what’s going on and at every level, from production all the way through to the food itself, that monitoring is extremely important for us to know what’s going on.

Mr. Tonko. I take the efforts obviously are very important to the public——

Dr. Woodcock. Yes.

Mr. Tonko [continuing]. And we are at least pleased to hear that there is that kind of review being conducted, but I would love to see efforts go forward to make certain that there is every bit of safety and consumer-oriented response so that we can move forward progressively.

Dr. Woodcock. Thank you.

Mr. Tonko. With that, I yield back.

Mr. Burgess. The gentleman yields back. The chair thanks the gentleman.

The chair recognizes the gentleman from Oklahoma, Mr. Mullin, 5 minutes for questions, please.
Mr. MULLIN. Well, I don’t know about the antibiotics in cattle, but I live on a farm and I am on three different antibiotics as we speak. I literally just got off Bactrim and I am on a Z–Pak and I have got another one that was prescribed to me yesterday. And so to say that they are overprescribed, I thank the Lord for them, but I will probably say you are accurate on that.

With that being said, the University of Oklahoma has done a phenomenal job on trying to close the gap on what they call the superbug, and they recently developed a new antibiotic to go after what a lot of people refer to as MRSA or a staph infection. But even with all that development, Dr. Woodcock, despite the recent success at the University of Oklahoma, are there concerns that new drugs aren’t being developed quickly enough to help close this gap?

Dr. WOODCOCK. Yes. There are major concerns because the microbes are kind of like the criminals. They’re always one step ahead of us, right, and if you expose people and you expose the bacteria to an antimicrobial, some of them will develop resistance. So we need a robust pipeline.

We have approved a number of antibacterials recently for MRSA infections, new ones, but the general pipeline of antimicrobials is not robust. It’s very fragile. We don’t just need very targeted antimicrobials, we need a broad set of antimicrobials for the future. And that’s still not happening, although there—you know, certainly there are discoveries being made.

Mr. MULLIN. So with the current crop of antibiotics out there, do you see where we are going to be able to catch up or we are going to continue to stay behind or get farther behind?

Dr. WOODCOCK. I think we need to be very concerned because it’s not the work of a year to catch up, it’s the work of decades. And these development programs—Dr. Burgess mentioned Pfizer earlier; they’re no longer in the space of development. These development programs were terminated by lots of companies several decades ago.

Mr. MULLIN. Due to?

Dr. WOODCOCK. Lack of economic incentives and the fact that at that time there was of course a broad range of antimicrobials available. And even though we could foresee resistance occurring in the future, the return on investment wasn’t there compared to, say, cancer or other fields.

Mr. MULLIN. Well, Dr. Woodcock, how long does it take, say, a company that is wanting to develop this, how long does it take them from when they start to when they can probably bring a product to the market?

Dr. WOODCOCK. If you start from discovery, probably 10 years.

Mr. MULLIN. At the cost of what?

Dr. WOODCOCK. The estimates are very controversial. Many people have said between $1 billion and $2 billion for a new molecular entity.

Mr. MULLIN. So is there a way to speed this up? I mean, if we are behind because, my goodness, I can understand why a company would be hesitant to invest $1–2 million on an——

Dr. WOODCOCK. Billion.
Mr. MULLIN. Billion, I am sorry, $1–2 billion on an antibiotic and it takes 10 years to bring it to market and the success rate is, I am sure, pretty low. Do you know what the success rate is on that?

Dr. WOODCOCK. For antimicrobials, it’s—if you start from discovery, it’s going to be one in many thousands, OK——

Mr. MULLIN. One in many thousands, so——

Dr. WOODCOCK. You start into entry into the clinic, it might be 1 in 10.

Mr. MULLIN. So what is the incentive for a company to do this? I mean, I am thinking as a business owner I am going, OK, I am going to invest $1–2 billion and I am going to have 1 out of 1,000—let’s just use that number—of a chance of it actually coming to market. Is there an incentive? Is there a way to bring this number down? Is there a way to help improve that?

Dr. WOODCOCK. Well, I would also add that we would urge you as a business owner once you develop this drug to make sure it’s used very narrowly and not widely used because otherwise resistance would develop.

Mr. MULLIN. Well, I agree with that, but you have got to get your money back.

Dr. WOODCOCK. I understand that.

Mr. MULLIN. Is the FDA looking into this to help ease those barriers, help speed that process up? Because we can all tell this is going to be a major problem, and so it seems like we should be working together on this.

Dr. WOODCOCK. Oh, yes. And we’ve been doing things for years. We have issued a number of new guidances on new pathways. We’re working with outside public-private partnerships on new end points, different ways to study the drugs, and then what was mentioned earlier, the limited population use that’s in the 21st Century Cures would be another way of streamlining the development programs.

Mr. MULLIN. Dr. Woodcock, thank you. I am out of time.

Mr. BURGESS. The gentleman yields back. The chair thanks the gentleman.

The chair recognizes the gentlelady from Illinois, Ms. Schaakowsky, 5 minutes for questions.

Ms. SCHAKOWSKY. This is exactly the conversation that I have been wanting to get into.

Dr. Woodcock, in conclusion you say “It is virtually undisputed that we are facing a public health crisis because of the rise of serious resistant infections and the simultaneous decline in R&D in this area.” What I am hearing is that there is not enough profit in addressing this problem. And that sets my hair on fire. If this is a worldwide public health issue and the reason that we cannot make progress is because—as have been called—our industry partners are unwilling to do that because there is not enough money,
then it seems to me exactly the space then that government needs to step in and deal with this.

I just don’t understand the word “incentives”—and there may be other ways besides money. I don’t know. But what are we talking about here, that these companies are getting out of the business, that the Pfizer are getting out of the business. There is just not enough dough here when at some point this could be just a worldwide problem of the bug that is going to kill, I don’t know, millions of people. Somebody answer me.

Dr. Bell. Well, I would say there are two problems. One is it’s very hard to discover and develop these——

Ms. Schakowsky. Right.

Dr. Bell [continuing]. OK, scientifically. And then once you get them on the market, we’re going to——everyone will ask them is don’t sell them, OK, don’t sell them very much because they’re too valuable to waste on—that was the paradigm in the past, and that’s why antimicrobials are so overprescribed, OK, is they were used for minor infections——

Ms. Schakowsky. Well, can I——

Dr. Bell [continuing]. And viruses——

Ms. Schakowsky [continuing]. Interrupt for a second? I think one of the other issues that contributes to that problem is TV advertising of drugs, which has created an atmosphere among consumers that I am in charge of my health, I am going to go to my doctor, I am going to say what I want, I will find a way to get that drug. I just wanted to add that. I think that is part of the culture that contributes to this problem. Anybody?

Dr. Hatchett. Thank you. It’s a critically important question. And I have seen an estimate that the market for antibiotics in the United States is about $40 billion. But of that $40 billion for that market, only about $4–5 billion is for drugs that are unpatented. So any new drug that enters the market enters a market where there are dozens of competing generic antibiotics. And so the new entries can’t charge a premium unless they can fully differentiate themselves from all of the other antibiotics that are on the market. And so it suppresses the ability to achieve profit for a new drug.

And you’ve heard the estimates of what it costs to bring a new drug to market, and so companies, to recoup their investment over many, many years have to see opportunities in the marketplace that they can achieve that return even almost just to a breakeven.

The model that BARDA has implemented in other areas where the market is failing to deliver public health requirements so against agents of bioterrorism or pandemic influenza, for example, we over the past decade have evolved a model where we provide substantial advanced research and development funding for products that have reached the stage of clinical development. So these are things that are being tested in human clinical trials. We also provide a market entry incentive, a pull incentive in terms of a procurement of the product. So for something that we’re developing for bioterrorism, we then buy a large quantity of it and put it into the strategic national stockpile so a person working under it has a guaranteed market commitment.

And the other thing that we provide, which is very, very critical, we found this to be extremely critical is we provide access to a core
of experts on all aspects of product development who can assist potentially smaller companies that don’t have all of this expertise in-house and to access to product development infrastructure. And so it’s a multi-legged stood in terms of the support that we provide.

It wasn’t until we put all of those components together for our bioterrorism threats, for pandemic influenza threats that we really started to see our program succeed. We think many of those elements are going to be required to overcome these adverse market courses that are leading to disinvestments.

Ms. SCHAKOWSKY. Well, I hope that bottom line isn’t that we have to look at the bottom line of for-profit companies to figure out whether we are going to protect the health of this planet.

Mr. BURGESS. The gentlelady yields back.

Let me if I could, I would like to ask a follow-up question because the Center for Medicare and Medicaid services yesterday put out a relatively lengthy proposed rule on the stewardship program. You have had a chance to familiarize yourself with the proposed rule that CMS put out. Now, the question is, once again, do we get the right balance between the regulatory burden and effective governance? So, again, I would just appreciate your thoughts on the proposed rule.

Dr. BELL. I haven’t actually seen the rule itself, Congressman, but we have been working with CMS around this concept for quite some time. They have already actually had previously issued some comments for similar kind of conditions of participation for long-term care. Now, this is the one for acute care.

So I appreciate your point about a balance between regulation and individual clinical judgment. In general, these conditions of participation, they’ve been working closely with us and they basically are meant to incorporate the core principles of stewardship that we published in 2014 for inpatient and 2015 for long-term care. So these are really just fundamental kind of necessary pieces of a puzzle so that a facility has a stewardship program that actually is able to influence the process.

And I will say also that this whole process of coming up with the core elements and CMS’s participation has really been very broadly supported in general by American Hospital Association and by lots of kind of industry partners. I think there really is a broad agreement now that the concept of helping physicians and facilities and patients prescribe wisely is really pivotal.

We’ve been talking a lot about drug development and what all the gaps are there, but really—and, as you’ve heard, I think this whole issue of antibiotic resistance is a long-term problem that has many components, and we really have to address them all in order to tackle it. And one of the pivotal components is this issue of stewardship, of getting serious about doing something about overprescribing, not stopping people from prescribing but being able to preserve the antibiotics that we have now. And that’s sort of about saving lives now, as well as these areas of prevention and diagnostics and new drug development.

So as I say, I’m not familiar with the specifics, but it has been really a very broad process that CMS has gone through and has collaborated quite closely with us.
Mr. Burgess. Dr. Woodcock, on the issue of stewardship—and you have mentioned in your opening statement in response to Mr. Tonko's question about involving the USDA and the veterinarian space in this. It is one thing to come down hard on the private practice doc in the United States for overprescribing antibiotics, and I probably include myself in that group that would feel put upon by some of these directions. But honestly, we can't compete with what is being used in feedlots.

Dr. Woodcock. Yes. Well, as I said, the Center for Veterinary Medicine has taken steps around that and secured commitments from those manufacturers of medically important antimicrobials that they will submit a supplement that will eliminate that use basically.

Mr. Burgess. And let me just—

Dr. Bell. If I could just add that the concept of stewardship and stewardship for veterinarians, in addition to stewardship for human doctors is something that the American Veterinary Medical Association has been quite interested in, and we've been providing them actually with a lot of tools that they could use with veterinarians. And actually we haven't spoken about companion animals, but this is another area actually where we really don't have a very good sense—

Mr. Burgess. Sure.

Dr. Bell [continuing]. Of what's happening, and we will be—

Mr. Burgess. Let me—

Dr. Bell [continuing]. Looking to establish something there.

Mr. Burgess. I am going to stop there for—I want to ask one other question, Dr. Woodcock, since we are speaking about animal products. The issuance under an emergency use authorization for a genetically modified mosquito in parts of the world that are affected by the Zika virus, why is that taking so long? Why is it so difficult? Why is a genetically modified mosquito having to go through a new drug application?

Dr. Woodcock. Well, that is out of my wheelhouse, and we'd have to get back to you on that particular question.

Mr. Burgess. OK.

Dr. Woodcock. It's not a drug—

Mr. Burgess. But my understanding, it is being treated as if it was a new drug application, so I appreciate that is not part of today's discussion, but I really do want to follow up with you on that, because I think it is an important issue.

Seeing no further members wishing to ask—you have a question? The gentlelady from Illinois just wants me to conclude, so I do want to thank all our witnesses and members who have participated in today's hearing. I remind members they have 10 business days to submit questions for the record, and I ask all the witnesses to agree to respond promptly to these questions.

With that, the subcommittee stands adjourned.

[Whereupon, at 12:01 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]
TO: Members, Subcommittee on Oversight and Investigations
FROM: Committee Majority Staff

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 “Combating 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. 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

Majority Memorandum for June 14, 2016, Subcommittee Oversight and Investigations Hearing
Page 2

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

---

7 Lena H. Sun, CDC Says ‘Nightmare Bacteria’ a Growing Threat, THE WASHINGTON POST, March 5, 2013.
8 Id.
9 Id.
to colistin, an antibiotic of last resort.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 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.”\textsuperscript{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.\textsuperscript{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.\textsuperscript{16} This amounts to nearly 47 million unnecessary prescriptions given out each year.\textsuperscript{17} Most of the unnecessary antibiotics are prescribed to treat respiratory

\textsuperscript{12} Colistin is not used at all in farm animals in the U.S.
\textsuperscript{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.
\textsuperscript{17} Id.
conditions such as the common cold, bronchitis, and other viral illnesses. Antibiotics are not effective against viral illnesses, but doctors sometimes 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. 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. About 13 percent of all outpatient visits in the United States result in an antibiotic prescription, which amounts to about 154 million visits annually.

Dr. Frieden has commented that overuse 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.

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. 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.

**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.

---

The last 30 years have marked a significant reduction in the discovery on new antibiotics. Currently, every antibiotic is a derivative of a type of antibiotic discovered from 1900 to 1984. 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.

In addition to the poor discovery prospects and gaps in scientific research, antibiotics are expensive to develop and offer a poor return on investment. 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. Historically, about 60 percent of drugs that enter phase 3 will be approved. 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. About half of those companies are small companies that have no products on the market.

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.
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 Antimicrobial Resistance (CARB) in response to an Executive Order issued by President Obama in September 2014. 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. Congress has increased funding for these initiatives by 57 percent over last fiscal year, for a total of more than $375 million.

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.”

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. In March 2016, the President’s Advisory Council on Combating Antibiotic-Resistant Bacteria issued “initial assessments” of the progress on the action plan.

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.” 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.” 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.

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.

---

37 Id.
38 Id.
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

---

43 The Centers for Disease Control and Prevention, *Core Elements of Hospital Antibiotic Stewardship Programs*, 2014.
46 Id.
drug candidates through early development, (3) provide business and drug development
guidance, and (4) decrease barriers to research and development of antibiotics.\footnote{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.\footnote{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.

\footnote{47}{Id.}
\footnote{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.}