

**PROMOTING THE DEVELOPMENT OF ANTIBIOTICS
AND ENSURING JUDICIOUS USE IN HUMANS**

HEARING
BEFORE THE
SUBCOMMITTEE ON HEALTH
OF THE
COMMITTEE ON ENERGY AND
COMMERCE
HOUSE OF REPRESENTATIVES
ONE HUNDRED ELEVENTH CONGRESS
SECOND SESSION

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PROMOTING THE DEVELOPMENT OF ANTI-BIOTICS AND ENSURING JUDICIOUS USE IN HUMANS

WEDNESDAY, JUNE 9, 2010

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

The subcommittee met, pursuant to call, at 10:09 a.m., in Room 2123 of the Rayburn House Office Building, Hon. Frank Pallone, Jr. [Chairman of the Subcommittee] presiding.

Members present: Representatives Pallone, Dingell, Eshoo, Green, DeGette, Capps, Matheson, Barrow, Christensen, Sarbanes, Waxman (ex officio), Shimkus, Whitfield, Murphy of Pennsylvania, Burgess, Blackburn, Gingrey and Barton (ex officio).

Staff present: Sarah Despres, Counsel; Ruth Katz, Public Health Counsel; Stephen Cha, Professional Staff; Eric Flamm, Professional Staff; Rachel Sher, Counsel; Alvin Banks, Special Assistant; Ryan Long, Minority Legislative Analyst; and Aarti Shah, Minority Professional Staff.

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

Mr. PALLONE. The subcommittee will come to order.

Today we are having a hearing on antibiotic resistance and the threat to public health, and I will recognize myself initially for an opening statement.

Today we are going to examine how we can best safeguard the effectiveness of antibiotics once they are on the market. We will also explore how we can ensure the adequate development of new safe and effective antibiotics. Later this year we expect to have a final hearing, essentially this is the second of three hearings, and the third or final hearing will be on antibiotic use in animal agriculture.

As we discussed in our first hearing, antibiotics are among the most significant medical innovations of the 20th century. The CDC lists control over infectious disease as one of its top 10 great public health achievements of the last century and mentions antimicrobials as crucial to that accomplishment.

Unfortunately, the potential of antimicrobials continues to be compromised. It is estimated that over 2 million people acquire bacterial infections in U.S. hospitals each year and 90,000 die as

a result of these infections. We should all be alarmed that at least 70 percent of these infections are resistant to at least one drug and more and more bacteria are proving to be resistant to the antibiotics currently on the market. Unfortunately, these resistant diseases are among the most predominant illnesses in the population including respiratory diseases such as pneumonia, food-related diseases including *E. coli* and salmonella, and hospital-acquired infections commonly known as MRSA.

As a matter of public health, it is imperative that we adopt a multi-pronged strategy to address antibiotic resistance. Today we will examine how we can best safeguard the effectiveness of antibiotics once they are on the market. We probably all heard stories of physicians that have overprescribed antibiotics to people who may have viral instead of bacterial infections, and while they may do this to safeguard against infection just in case, the overuse actually puts us all at risk. Patients also share blame. How many of us know someone that stopped taking their antibiotics once they felt better, even if they didn't finish the treatment.

Our experts will also explore how we can ensure the adequate development of new safe and effective antibiotics on the market. It is a challenging situation because unlike some pharmaceuticals which are used to treat chronic illnesses, there is not a clear return on investment for antibiotics. Antibiotics are unique because not only are they used for short periods of time per illness, but the more they are used, the less effective they become. So in order to preserve their effectiveness, we as a society should all share the goal that they be used as rarely as possible. This is obviously not the business model that companies dream of, however, and I would like to welcome all of our witnesses today including government representatives from the FDA and BARDA and also our private witnesses from the Infectious Disease Society of America, the American Medical Association, the American Academy of Pediatrics, and Cubist Pharmaceuticals. The witnesses will undoubtedly share key information related to our mutual goal of protecting the public from antibiotic resistance.

I would like to now recognize our ranking member, Mr. Shimkus, and also thank you for your cooperation in putting this together today. I know it has not been easy for the last 24 hours, but thank you.

OPENING STATEMENT OF HON. JOHN SHIMKUS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Mr. SHIMKUS. Thank you, Mr. Chairman, and we want to welcome our witnesses both in this panel and the next, and this is an important issue. This is the second in a series that we also feel is very important.

Antimicrobial drugs have provided tremendous benefit for the public health over the last half century. In order to ensure it remains so, we must continue to promote appropriate and effective use and the uses we already have. Overuse and misuse can limit the effectiveness and make outright resistance grow even faster. The other half of the equation is research and development and product development which are mainly concerned over the prospect of new drugs coming online. We know the cupboard is almost bare,

and of the limited drugs in development, most of them, if not all, will never see approval. Any investment in antibiotics is not likely to match that of traditional drug development and there remains an uncertain approval process when it comes to FDA. The FDA must continue to work on providing confidence and clarity so we can encourage the development of new antibiotics.

And as I talked before the hearing, we all have great respect for the work that the FDA does and it is the gold standard in the world but many of us are concerned that we are asking them to do too much with limited resources. Those of us who aren't in the business of increasing resources would want to help you make the job more efficient and directive. That is why I have always been a risk-based person, that that is where our money should go, and we will continue to work in that direction, but we do appreciate you being here.

Mr. Chairman, I will be brief but I will also just raise my issue of the concern that we need a hearing on the new health care law. The President used yesterday his bully pulpit to talk about the benefits of the law. We still have yet to have a hearing on it, and I think it is probably time. If there are things the President thinks are important and is willing to go out to the American public to profess the benefits, we ought to be able to talk about those benefits here. We also should talk about some of the challenges. We did have our Republican health solutions group meet, as I discussed in the last hearing, and during that hearing Dr. Todd Williamson testified on behalf of the Coalition of State Medical National Specialty Societies representing more than 80,000 physicians from across the country, and his testimony said, "The most significant cost of the new health care law will be to our patients. They will suffer decreased access to the doctors and care they need. My sickest and most vulnerable patients will suffer the most because of a depleted pool of physicians while the government continues to expand eligibility for its underfunded programs." In the State of Texas, 300 physicians have already stopped seeing Medicare patients over the last 2 years. Is Texas a snapshot of what is to come for the rest of the Nation when 15 percent cuts go into effect? And when it comes to Medicaid, we know the situation is even worse for physicians, in some cases, paying them 50 percent of what private insurance does. But the health reform law sets out to force millions of more Americans into Medicaid. We will face similar results when it comes to access and quality of care for patients. The State of Illinois is \$12.8 billion in debt, and Medicaid already consumes one-third of the spending for the increased cost of these new Medicaid populations.

Just yesterday, we had in the papers talked about N Health, which sells HSA high deductibles to employers recently announced it will terminate all its customers by December 31, 2010, because it cannot survive the health care law mandates and regulations. Then there is American National Insurance Company, which similarly announced two subsidiaries, American National Life Insurance Company of Texas and Standard Life, an accident insurance company, won't sell health insurance to people in the individual market after June 30, 2010, because of the health reform law. Can we really tell these people this if you like what you have you can

keep it when these companies go out of the business as the President promised to the American people. And it is only June of 2010. The full effects of this law won't go into effect until 2014. Are these problems only the tip of the iceberg?

So once again, Chairman, I certainly have an appreciation for our hearing today but we will continue to raise the health reform law and call on you for formal hearings to discuss the many issues both positive as the President promoted yesterday and negative, these health insurance companies leaving the market, what is working and what needs to be address before it is fully implemented.

Thank you, Mr. Chairman. I yield back my time.

Mr. PALLONE. Thank you, Mr. Shimkus.

Our chairman of the full committee, Mr. Waxman.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you very much, Chairman Pallone, for calling this second of a series of hearings that we are having on antibiotic resistance, which is a growing and dangerous threat to the public health and it is an issue that deserves the full and complete attention of this committee.

At our first hearing, we learned about the impact of antibiotic resistance on human health, and today we will continue that discussion, but also focus on two important and directly related issues: the preservation of effective medicines that already make up our antibiotics drug arsenal, and the development of new antibiotics to fight resistant bugs.

By definition, this is an inherently difficult goal to achieve. After all, the very use of antibiotics leads to the development of pathogens that can no longer be treated by those antibiotics. In this case, rather than use it or lose it, with antibiotics it is use it and lose it. Already untold numbers of Americans die or are infected each year by antibiotic-resistant microbes. We pay a high price in other ways as well—additional hospital stays, hospital readmission and increased doctor visits. These will add unnecessarily to the Nation's annual health care bill.

Our hearing in May made clear that it will take a multi-pronged approach to overcome this very serious and very present problem. Today we will focus on two such strategies, a reduction in the inappropriate use of antibiotics and the expansion of the antibiotic product line and market. I believe that we must pursue both lines of attack. We simply must find ways to cut back on both the overuse and misuse of these drugs.

At the same time, we need to ensure the existence of a market environment that encourages the development and commercialization of new safe and effective antibiotics to treat those pathogens resistant to existing antibiotics. Such an environment does not appear to appear to be in place today.

As we consider possibilities for market incentives, we must not lose sight of the potential impact those incentives may have on patients, especially if new antibiotics are more expensive than the patients can afford to buy.

The written testimony we have already received lays out a variety of approaches to meet these objectives. I look forward to hearing more about them from our witnesses today. As we do, I hope we can continue to work on a bipartisan basis towards a public-private plan of action to address the overall and pressing antibiotic resistance problem that we now face.

I thank the witnesses for their testimony and look forward to hearing from them. Thank you, Mr. Chairman.

[The prepared statement of Mr. Waxman follows:]

**Statement of Rep. Henry A. Waxman
Chairman, Committee on Energy and Commerce
“Promoting the Development of Antibiotics and Ensuring Judicious
Use in Humans”
Subcommittee on Health
June 9, 2010**

Thank you for holding this second in a series of hearings on antibiotic resistance – a growing and dangerous threat to the public health. It is an issue that deserves the full and complete attention of this Committee.

At our inaugural hearing, we learned about the impact of antibiotic resistance on human health. Today, we will continue that discussion, focusing on two important and directly related issues: the preservation of effective medicines that already make up our antibiotic drug arsenal and the development of new antibiotics to fight resistant bugs.

I understand that our next hearing on this topic will examine antibiotic use in animal agriculture, an area of great interest to many Committee members.

But today, we want to concentrate on the human dimension of antibiotics and the importance of ensuring that, both here in the U.S. and around the globe, people keep on benefiting from these life-saving treatments.

By definition, this is an inherently difficult goal to achieve – after all, the very use of antibiotics leads to the development of pathogens that can no longer be treated by those antibiotics. In this case, rather than “use it or lose it,” with antibiotics it is “use it **and** lose it.”

And “lose it,” we are. As was reported at our first hearing, for a variety of reasons, we are at great risk of backtracking on much of the progress that has been made in fighting infection and subsequent disease. Already untold numbers of Americans die or are infected each year by antibiotic resistant microbes. We pay a high price in other ways as well: additional hospital stays; hospital re-admissions; and increased doctor visits. These all add – unnecessarily – to the nation’s annual health care bill.

Our hearing in May made clear that it will take a multi-pronged approach to overcome this very serious and very present problem. Today, we will focus on two such strategies: a reduction in the inappropriate use of antibiotics and an expansion of the antibiotic product line and market.

I believe we must pursue both lines of attack. We simply must find ways to cut back on both the overuse and misuse of these drugs. Patients cannot expect to get antibiotics every time they come down with a cold and physicians should only prescribe them when they are truly necessary.

At the same time, we need to ensure the existence of a market environment that encourages the development and commercialization of new safe and effective antibiotics to treat those pathogens resistant to existing antibiotics. Such an environment does not appear to appear to be in place today.

As we consider possibilities for market incentives, we must not lose sight of the potential impact those incentives may have on patients – new antibiotics are worthless if people cannot afford to buy them.

The written testimony we have already received lays out a variety of approaches to meet these twin objectives, and I look forward to hearing more about them from our witnesses today. As we do, I hope we can continue to work, on a bipartisan basis, towards a public-private plan of action to address the overall and pressing antibiotic resistance problem that we now face.

I thank the witnesses for their testimony and look forward to hearing from them.

Mr. PALLONE. Thank you, Chairman Waxman.
The gentleman from Kentucky, Mr. Whitfield.

OPENING STATEMENT OF HON. ED WHITFIELD, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF KENTUCKY

Mr. WHITFIELD. Thank you, Mr. Chairman, and I also want to thank the witnesses for being with us today on this very important subject. Certainly the American people are very much focused today on access to health care, quality of health care as well as cost of health care, and the subject matter that we are going to discuss today is one very important component of that.

It has already been stated that 2 million people roughly acquire infections in hospitals and about 90,000 of those die each year. Seventy percent of the hospital-acquired infections are caused by bacteria that are resistant to particular drugs most commonly used.

We certainly understand that the process for developing clinical trials at the FDA is extremely complex and we look forward to the testimony today to explore opportunities to make it less complex but also ensuring safety. I know it is my understanding that there are about 15 antibiotics that are in the pipeline today at FDA for approval, and I am not sure how I know this but evidently we don't think there is much chance that many of those are going to be approved, but we do need to explore ways to provide incentives for pharmaceutical companies as well as trying to make the system less complex but also ensuring safety, and I am delighted we are having this hearing and look forward to the testimony of all our witnesses.

Mr. PALLONE. Thank you, Mr. Whitfield.

Mr. WAXMAN. Mr. Chairman, before you recognize——

Mr. PALLONE. Yes?

Mr. WAXMAN. I just want to make a unanimous consent request, which I should have made. It is to put into the record a statement by Dr. Michael T. Flavin, chairman and chief executive officer of Advanced Life Sciences prepared for the record for this committee.

[The information was unavailable at the time of printing.]

Mr. PALLONE. Without objection, so ordered. Thank you, Mr. Chairman.

And next is our chairman emeritus, Mr. Dingell.

OPENING STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. DINGELL. Mr. Chairman, thank you for holding today's hearing on what is a growing and real public health crisis.

Two months ago, we had a hearing on the basics of antibiotic resistance during which one of our witnesses, Dr. Thomas Frieden, director of the Centers for Disease Control, stated that we are moving into a post-antibiotic world. He warned that there may be soon no clinical treatments for some infections. This is a very real and frightening crisis.

Today, 19,000 people die a year of multi-drug-resistant MRSA. Our soldiers are coming home from Afghanistan and Iraq with acinetobacter, which is often resistant to at least three classes of

antibiotics, and hospital-acquired antibiotic-resistant infections cost our health care system up to \$34 billion a year. Imagine what we are going to have to do when we find that we cannot deal with serious diseases the way we can now with antibiotics.

I want to thank our witnesses today for joining us, and I hope that from our witnesses we can begin to get this country on a track where we practice sound evidence-based public policy that can make us better stewards of antibiotic use and of our future and how we can assist all of the stakeholders in this public health issue. More specifically, we need to learn, amongst other things, how do we prevent the spread of infections that require antibiotic treatments? How do we best educate patients and doctors about judicious and prudent use of antibiotics? And finally, how do we improve upon the current incentives and regulatory structures that bring new antibiotics and diagnostic tests into the marketplace?

The growing number of bacteria resistant to antibiotics is frightening and will become more so. Even more frightening is the thought that our health providers and general public have not realized the magnitude of the problem that we face with resistant bacteria. Less-effective treatments for bacterial infections mean longer-lasting illnesses, more doctor visits, extended hospital stays, the need for more-expensive and toxic medications, and in a growing number of cases, death of the patient. Our children are at a greater risk because they have the highest rates of antibiotic use. We have to be smart about our approach in addressing this issue, and today's hearing should provide great insight and direction, and it is time that we recognize the urgency of this situation.

I thank you, Mr. Chairman, and I yield back the balance of my time.

Mr. PALLONE. Thank you, Chairman Dingell.

Next is our ranking member of the full committee, Mr. Barton.

**OPENING STATEMENT OF HON. JOE BARTON, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. BARTON. Thank you, Mr. Chairman. It is always good to have a hearing looking to the future. We look forward to the testimony today of the individuals who are going to testify about our antibiotics and what we are doing to make sure that the next generation of antibiotics continues to be as effective as the current generation is.

We also look forward, Mr. Chairman, to having you and the full committee chairman at some point in time schedule some hearings on the new health care law. We find daily evidence that it is not what it appears to be. HHS has already missed numerous deadlines. We have had the CBO and other budget agencies come out that instead of saving money it is going to cost hundreds of billions, perhaps a trillion dollars more than estimated. The President must think it is in some trouble. He had a campaign-style rally this week trying to drum up support. We need to do due diligence, and if there are things in the law that need to be changed, the sooner we get about changing them, the better it will be for the American people. So I hope that that happens sooner rather than later.

But in terms of today's hearing, we do look forward to the testimony from our witnesses because this is an issue that does deserve some attention and we appreciate you giving it to us.

With that, I yield back, Mr. Chairman.

[The prepared statement of Mr. Barton follows:]

Opening Statement
Honorable Ranking Member Joe Barton
Subcommittee on Health
Hearing on Antibiotic Resistance
Wednesday, June 9, 2010 – 10:00 AM

Mr. Chairman, I would like to welcome the witnesses and thank them for testifying on the need to develop the next generation of antibiotics.

Antibiotics are 20th century miracle drugs that everybody in the 21st century takes for granted until they don't work. The buildup of resistance to the current generation of powerful antibiotics is an important public health issue, and I look forward to hearing from our distinguished witnesses about how we can get newer, better antibiotics on the market.

But as you know Mr. Chairman, Congress also has an urgent need to hear about what's going on with the new health care law. The news is full of stories of missed deadlines and complex problems, but even if we each do our own detective work, it seems unlikely that we can match the power of the full Committee to create an accurate picture of what's going on.

Republicans on the Committee have been asking for a hearing on the new health care law, both before the law got enacted and as it is being implemented. In response to some of our previous requests, in which we questioned holding certain hearings while failing to hold oversight hearings on the health care law, the full Committee Chairman stated that this Subcommittee could walk and chew gum at the same time.

Well, Mr. Chairman, it is time for this Subcommittee to prove that it can actually do that. We have a responsibility to explore the effects of the new law, both the good ones and the bad ones. Indeed, last week, Ranking Member Shimkus, Ranking Member Burgess, and I wrote to President Obama highlighting the mounting evidence that many Americans will soon lose their employer-based health insurance thanks to what the White House proudly calls its “insurance reform” law. During the debate on health care, President Obama promised that if Americans liked their current plan, they could keep it. Now it looks like the President’s promise was a public relations statement. Internal documents of four major American companies produced at the request of Chairman

Waxman show these companies considering ending employer-sponsored care for their employees.

And a recent study conducted by a former director of the Congressional Budget Office concluded that the incentives in the health law could lead employers to drop employer-based health insurance for as many as 35 million Americans. Mr. Chairman, did the President's promise that Americans could keep their current health plan not apply to these Americans? It is time that we had witnesses before us to explain the true effects of the law we just enacted.

It is also true that the Obama Administration is having major problems meeting the deadlines and responsibilities of this massive law. On June 21st, the Administration faces another major deadline when it must establish a high-risk

health insurance pool to cover individuals with pre-existing conditions who have been without coverage for more than six months. Basic questions about the structure of the program remain unanswered, and we have no evidence that the Administration is on target to meet that deadline, partly because we have had no hearing, no witnesses, and no documents. All we have is a promise, like the one where people were supposed to be able to keep the insurance they liked.

If this Committee did a better job of providing oversight of the Administration and held hearings on the new law, I think the Administration would be more likely to take its obligations under the law more seriously, and people would be more likely to change their opinions on the value of its promises.

Thank you, Mr. Chairman. I do believe the subject of today's hearing is important, and we must develop policies that create an environment where new therapies are developed. I do hope, however, that we can figure out a way to deal with more than one problem at a time. I yield back the balance of my time.

Mr. PALLONE. Thank you, Mr. Barton.
The gentlewoman from California, Ms. Eshoo.

OPENING STATEMENT OF HON. ANNA G. ESHOO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Ms. ESHOO. Thank you, Chairman Pallone, for holding this hearing on antibiotic resistance, which is a growing concern for scientists, for the medical community, for patients and certainly for policymakers. I want to extend a warm welcome to both Drs. Woodcock and Robinson and thank you for the work, the important work that you do.

The discovery of antibiotics transformed medical care in the 20th century. Many bacterial infections which were once deadly are now treatable illnesses. People no longer die from minor cuts, from ear infections or pneumonia. Antibiotics treat infections on the battlefield, after surgeries and in doctors' office across the country.

But antibiotics are not the universal remedy to all illnesses. The widespread and inappropriate use of antibiotics leads to dangerous antibiotic-resistant bacteria, and due to the relatively low side effects of antibiotic use, physicians often prescribe them for maladies such as flu or the common cold. Antibiotics cannot treat these illnesses and their misuse leads to the rise of antibiotic-resistant strains of illnesses, and as these strains appear, some patients may have nowhere to turn when they have exhausted their antibiotic options.

Attempts to reduce antibiotic resistance must be comprehensive. We should curb the overuse of them and at the same time encourage the development of new antibiotics to keep pace with new strains of resistant infection. Antibiotic resistance has the potential to become a significant public health crisis. I am especially interested to learn about what role BARDA and Project BioShield may play in promoting the development of new antibiotics.

So my thanks to the FDA for not only testifying today but for your ongoing, I think extraordinary work, and I look forward to working with all the members of the committee to address the issue of antibiotic resistance.

I yield back, Mr. Chairman.

[The prepared statement of Ms. Eshoo follows:]

**Statement of the Honorable Anna G. Eshoo
Committee on Energy and Commerce, Health Subcommittee
Hearing, "Promoting the Development of Antibiotics and Ensuring
Judicious Use in Humans"
June 9, 2010**

Thank you, Mr. Chairman for holding this hearing on antibiotic resistance, a growing concern for scientists, the medical community, patients, and policy makers.

The discovery of antibiotics transformed medical care in the twentieth century. Many bacterial infections which were once deadly are now treatable illnesses. People no longer die from minor cuts, ear infections, or pneumonia. Antibiotics treat infections on the battlefield, after surgeries, and in a doctor's office.

But antibiotics are not the universal remedy to all illnesses. The widespread and inappropriate use of antibiotics leads to dangerous antibiotic-resistant bacteria. Due to the relatively low side-effects of antibiotic use, physicians often prescribe them for maladies such as the flu or the common cold. Antibiotics cannot treat these illnesses and their misuse leads to the rise of antibiotic resistant strains of illnesses. As these strains appear, some patients may have nowhere to turn when they've exhausted their antibiotic options.

Attempts to reduce antibiotic resistance must be comprehensive. We should curb overuse of antibiotics, and at the same time encourage the development of new antibiotics to keep pace with new strains of resistant infection. Antibiotic resistance has the potential to become a significant public health crisis. I'm especially interested to learn what role BARDA and Project Bioshield may play in promoting the development of new antibiotics.

My thanks to the FDA for testifying today and I look forward to working together to address the issue of antibiotic resistance.

Mr. PALLONE. Thank you.

Next is the gentleman from Texas, Mr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman. It is an important hearing, important witnesses. I am going to submit my statement for the record and reserve time for questions.

Mr. PALLONE. Thank you.

Our vice chair, the gentlewoman from California, Ms. Capps.

OPENING STATEMENT OF HON. LOIS CAPPS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mrs. CAPPS. Thank you, Mr. Chairman. Thank you for holding this hearing, and welcome to our witnesses in both panels.

A few weeks ago, as others have recalled, we held an informative hearing on the subject of antibiotic resistance. I think this hearing is a logical follow-up to the many questions that arose at that time. Most importantly, how do we balance the simultaneous need to halt the development of antibiotic resistance while incentivizing the development of effective antibiotics and ensuring patient compliance? I think we will learn from our witnesses today that the solution lies in a multifaceted approach that relies on, one, improving our basic research capabilities; two, incentivizing the private sector to invest in the necessary research and development; three, better educating health professionals on the most effective prescription of antibiotics and the ways to do this; and last, and I am sure there are more, making our public more aware of the ways they minimize risk of infection, prevention, in other words.

So I look forward to hearing from our witnesses on their suggestions for achieving these objectives and how we can develop the most appropriate policies to implement them, and I yield back the balance of my time.

Mr. PALLONE. Thank you.

Next is the gentleman from Georgia, Mr. Gingrey.

OPENING STATEMENT OF HON. PHIL GINGREY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Mr. GINGREY. Thank you, Mr. Chairman.

Antibiotics are a critical treatment for many bacterial infections and oftentimes their usage saves lives. Unfortunately, overutilization of antibiotics makes it more likely that bacterial resistance to antibiotic therapy will develop. Staying ahead of bacterial resistance to antibiotics is vital to our health care system. We can do that in part by educating medical providers on the proper use of these drugs. Many illnesses can be treated by proper diagnosis and over-the-counter remedies rather than relying on prescribing antibiotics. In many instances, it is appropriate and does not require much time or cost to take a culture in order to properly identify a patient's condition. If we are to combat bacterial infections, taking the necessary steps to identify appropriate cases for antibiotics is an important first step.

Mr. Chairman, we must also be aware that patient demand plays a big part in the overutilization of antibiotics. In many instances, patients will request an antibiotic from their provider because they are convinced it will cure common infections faster than over-the-counter treatment, and that is certainly not always the case. Hav-

ing spent time in general practice during my 30-year medical career, I understand how patient demands can influence provider decision. Therefore, any education efforts should include those aimed at informing patients of the dangers of overusage of antibiotics.

Unfortunately, no amount of education is going to stop antibiotic resistance. New forms of antibiotics must be available if we are to effectively deal with this emerging problem. Today the high cost of drug development and short treatment courses have caused a decreasing number of companies to pursue antibiotic development. In other words, their success has led to the fact that there is a shortage now of antibiotics. Any solution geared towards addressing future bacterial infections must ensure that proper incentives are identified and supported that will encourage greater antibiotic development. This committee should not shy away from reviewing the pathway of drug development, from drug discovery all the way through to licensing. My hope is that a balanced and thorough review of the antibiotic market will help ensure that we properly identify any disincentives that may exist with regard to the production of new antibiotics and are better prepared to promote incentives that may reverse this current trend. I believe this problem is one that can best be solved by encouraging industry and government to work together to find the solutions that our future health needs require.

Mr. Chairman, with these thoughts in mind, I would like to thank you for holding today's hearing on this important and growing issue. I look forward to hearing the expert testimony from our distinguished panel of witnesses, and I yield back the balance of my time.

Mr. PALLONE. Thank you.

The gentleman from Utah, Mr. Matheson.

**OPENING STATEMENT OF HON. JIM MATHESON, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF UTAH**

Mr. MATHESON. Thank you, Mr. Chairman, for holding this hearing today, and thanks to the witnesses as well.

As you are aware, I have reintroduced legislation in this Congress, H.R. 2400, the Strategies to Address the Antimicrobial Resistance Act, or the STAR Act, as the acronym is, which I believe is a comprehensive piece of legislation to strengthen our Nation's response to pathogens that are increasingly resistant to antibiotics. Senators Sherrod Brown and Orrin Hatch introduced the companion bill in the 110th Congress. Over 25 health care stakeholders support this legislation, a number of which will testify today in this hearing. H.R. 2400 provides strategies and authorizes critically needed funding to strengthen federal antimicrobial resistance surveillance, prevention and control and research efforts. It also strengthens coordination within the Department of Health and Human Services' agencies as well as across other federal departments that are important to addressing antimicrobial resistance and considers opportunities to address this issue globally.

The STAR Act provides a rare opportunity to bring many partners together to protect public health. This legislation was developed with input from infectious disease experts and leaders in public health and provides authority for the federal government to

combat antimicrobial resistance in four ways. Number one: It reauthorizes the antimicrobial resistance task force, establishing an advisory board of outside experts and an antimicrobial resistance office reporting to the Secretary of Health and Human Services, whose director will coordinate government efforts to combat antimicrobial resistance. Number two, it creates an antimicrobial resistance strategic research plan as well as establish the antimicrobial resistance surveillance and research network. Number three, the bill calls for collecting available and relevant data to allow government to better address the antimicrobial resistance problem, and fourth, it establishes demonstration projects to encourage more appropriate use of existing antibiotics.

Mr. Chairman, as you are aware, our committee has had a critical role in establishing the foundation of work for this issue. Our chairman emeritus, Mr. Dingell, requested a report on the impact of antibiotic-resistant bacteria in the 103rd Congress. In the 106th Congress, Chairman Stupak introduced legislation to direct the Secretary of HHS to establish the antimicrobial resistance task force. In the 10th Congress, several members of this committee joined Senator Sherrod Brown, who at that point was a member of this committee, to introduce legislation to provide funding for the top priority action items of the public health action plan.

I provided this brief snapshot of this history for my colleagues to show that while some work has been accomplished, the war against resistance to infection looms large for our Nation's public health, and to be clear for my colleagues on both sides of the aisle, this is a public health emergency that in the year 2007 alone infected more than 94,000 people and its estimated cost to our health care system was millions of dollars.

I look forward to the hearing today and hearing from our witnesses and look forward to doing whatever we can to work with this committee to help move this legislation forward. I yield back my time.

Mr. PALLONE. Thank you, Mr. Matheson.

The gentleman from Pennsylvania, Mr. Murphy.

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

Mr. MURPHY OF PENNSYLVANIA. Thank you, Mr. Chairman.

Two million people will acquire infections in hospitals this year. Between 90,000 and 100,000 will die. The costs will be about \$50 billion to treat them. And by those numbers, so far today this year, 44,133 people have died from a hospital-acquired infection.

Although today we are talking about the overprescribing of antibiotics, let us understand the most effective antibiotic is the one you do not have to prescribe. Prevention does work. Hospitals that vigorously gather data on infection rates and enforce infection controls see decline in infection rates but many doctors, families, hospital staff do not do this, and that is the root of one of our problems that we have to address.

Over time, I have introduced over repeated Congresses legislation to require hospitals and clinics to report their infection data. Unfortunately, we have not moved it forward at all in committee

and has not moved anywhere in the House. This means that hospitals are not required to gather information nor report their infection rates, and as such, a lot of people are dying because we are not paying attention to it.

The solutions don't require great science or approval from the FDA. It means that people that come near a patient have to wash their hands, use sterile equipment, wear clean clothes such as gowns or gloves or masks, clean up before and after procedures, use antibiotics before and after surgery, and have close monitoring of infection rates and quick reaction time when infections occur.

So I have reintroduced this bill once again, H.R. 3104. I hope that in addition to dealing with bacteria that are resistant to antibiotics, we also begin to deal with resistance by caregivers to passing legislation that requires them report infection rates. To me, it is incomprehensible that the very providers who are out there saying we need to reduce infection rates are the ones opposed to finding out what those infection rates are. It is reprehensible that on one side of our mouth we are saying we want people to live and out of the other side of the mouth we are saying people don't tell anybody that we are not doing a very good job about it. I hope that sometime this committee will consider this legislation, require hospitals and clinics to begin to look at these rates and report them, and in so doing, I might add, when hospitals do this, they save lives. It is repeatedly demonstrated. And once again, the most effective antibiotic is the one you don't have to use. I yield back.

Mr. PALLONE. Thank you.

The gentlewoman from the Virgin Islands, Mrs. Christensen.

OPENING STATEMENT OF HON. DONNA M. CHRISTENSEN, A REPRESENTATIVE IN CONGRESS FROM THE VIRGIN ISLANDS

Mrs. CHRISTENSEN. Thank you, Chairman Pallone. Good morning.

As I read the testimonies last night and reflected on the first hearing with Drs. Frieden and Fauci, I kept thinking that we are supposed to leave a better world for our children than we have and there are many events that bring this into question and the issue of the antibiotic resistance which threatens to set the treatment of infectious diseases back into the Dark Ages is one of them. Dr. Frieden's and Dr. Fauci's testimony were very informative, and the witnesses we will hear from today will add to our understanding of the issue and to their recommendations.

As a family physician like my colleague over here, who practiced for over 20 years, I know the pressure that doctors are under to prescribe antibiotics and how difficult it is to have a patient continue on their regimen once they start to feel better, and those are but two of our challenges. The fact that only five out of several hundred drugs in the pipeline are antibiotics speaks volumes about the level of the crisis and the need to incentivize the pharmaceutical industry, something I recall not doing very well initially with BioShield but greatly improving on in 2006 with BARDA.

This is a multifaceted problem in which everyone from the patient to the provider and all the health care workers, the Department and Congress have an important role to play. We have several agencies and pieces of legislation with which we begin to ad-

dress the crisis and I look forward to what our witnesses have to say about them.

I want to thank you, Chairman Pallone and Ranking Member Shimkus for this hearing and the witnesses for their presence and for their very informative testimonies. Thanks.

Mr. PALLONE. Thank you, Mrs. Christensen.

I just wanted to yield briefly to our ranking member, Mr. Barton, for a personal point.

Mr. BARTON. I want to make a point of personal privilege, Mr. Chairman. Congresswoman Blackburn, whose birthday was yesterday, is smiling amongst us and she has had the great foresight to hire my stepdaughter or employ my stepdaughter as one of her interns, Lindsay Taylor, who is a junior at the University of Texas majoring, I believe, in business with a minor in marketing, and she did some of the work to prepare for the hearing today. So I want to introduce Marsha's intern and my stepdaughter Lindsay Taylor to the committee. Wave.

Mr. PALLONE. Thank you, and welcome.

Mr. BARTON. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. Welcome. And happy birthday to you also, Marsha.

Next is—actually next is the gentlewoman from Tennessee, Ms. Blackburn.

OPENING STATEMENT OF HON. MARSHA BLACKBURN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TENNESSEE

Mrs. BLACKBURN. Thank you, Mr. Chairman.

Welcome to those that are here today and thank you for the work that you have done in preparation for coming to us. Mr. Chairman, I thank you for the hearing today.

An interesting little tidbit as we prepared for this. According to the Tennessee Department of Health, the antibiotic resistant rates in Tennessee are among the highest in the Nation, and we know that this has come from overuse and misuse of antibiotics and it has contributed to this. This is something we have been fighting in our State for a long time as prescription use was higher than it should be. We know that it is a looming public health crisis, and it is of concern to us when we look at the rising incidence of drug-resistant bacteria, and we are concerned about the stagnant R&D of new therapies to treat some of these new infections.

It is alarming that medical professionals have very few resources to treat some of these patients as demand far outpaces supply of the antimicrobials. While prevention is key, not every infection is preventable, and we understand that but there is a growing concern about R&D, and it concerns me that there are only a few small private companies that are investing in R&D and putting their money into that and developing the new therapies that are needed, and we know it is difficult to hit a moving target, and as the antimicrobial pathogens constantly mutate, resulting in long-term R&D investment needs, and also realizing that for many of these there is a short-term usage.

And the other thing we are concerned about and that we hear from our medical community about is uncertainty from the FDA.

So as we go through the hearing today, those are points that we are going to want to cover with you, the concern about R&D, the concern about uncertainty with the FDA, and then also just the antibiotic resistance rates that we see in our State.

I thank you, and I yield back.

Mr. PALLONE. Thank you, Ms. Blackburn.

And I guess last, although I am not sure, is the gentlewoman from Colorado, Ms. DeGette.

OPENING STATEMENT OF HON. DIANA DEGETTE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO

Ms. DEGETTE. Thank you very much, Mr. Chairman. At least you didn't say I was last and least. I will submit my opening statement for the record.

I just want to point out a couple of facts that are even more disturbing than some of the facts we have heard from the members. One-third of the world's population is infected with TB, and in 2008 multidrug-resistant TB accounted for 5 percent of all tuberculosis cases, which is the highest percentage recorded to date, and even more frightening is the emergence of extensively drug-resistant tuberculosis that is resistant to all major TB drugs available. In the United States, 70 percent of the 2 million who die from hospital-acquired infections were infected with strains resistant to at least one antibiotic, and according to the CDC, \$1.1 billion is spent annually on unnecessary antibiotic prescriptions for adult upper respiratory infections. Those billions of dollars could be spent on developing new antimicrobials, not needlessly encouraging antibiotic resistance.

Unfortunately, antibiotic resistance will never go away because bacteria have an incredible capacity to evolve and multiply. Bacteria have existed on earth a thousand times longer than we have and can undergo 500,000 generations in the time it takes humans to undergo one generation. And so really, all the members today agree that we need to proactively confront antibiotic resistance. We can't eliminate it but what we can do is significantly reduce the rate and spread of antibiotic-resistant pathogens.

So everybody has noted it is important that we use antibiotics prudently, but prudent use alone is not enough. We need a multi-pronged approach that has regulation, surveillance, research and obviously new discoveries must rigorously be pursued in parallel. In addition, while it is not the topic of the hearing today, we need to look very closely at overuse of antibiotics in agriculture because that is another big problem that we face.

So it is a multi-pronged problem. I am glad, Mr. Chairman, you are looking at it in a multiple series of hearings, and since I am the last member, I am going to yield back the balance of my time so we can hear from our distinguished witnesses. Thank you.

[The prepared statement of Ms. DeGette follows:]



**Congresswoman Diana DeGette
Opening Statement
Subcommittee on Health Hearing:
“Promoting the Development of Antibiotics and Ensuring Judicious Use in Humans”
June 9, 2010, 10:00 A.M.**

On August 24, 1940, two Oxford University researchers published a revolutionary medical triumph in the scientific journal *The Lancet*. Howard Florey and Ernst Chain’s attempts to purify the active penicillin agent first observed by Alexander Fleming 12 years earlier had finally paid off. Mice infected with hemolytic *Streptococci* that were treated with the purified penicillin survived while their untreated counterparts did not.

Shortly afterward Florey flew to the United States to garner research support for mass production of penicillin. His diligence paid off. As the USDA initiated penicillin production efficiency and scale-up efforts, Florey and his colleagues successfully solicited industry buy-in. These collaborations between researchers, government, and industry, proved fruitful and ultimately spared the lives of thousands of World War II soldiers.

The work of doctors Fleming, Florey, and Chain earned them a Nobel Prize in 1945 and the world its first bacteria-fighting antibiotic.

Nearly a century after Flemings original observation, scientists have identified additional, though relatively precious few antibiotics suitable for human medicine. In this time we have also come against increasing numbers of antibiotic resistant bacteria.

One-third of the world's population is infected with tuberculosis or TB. In 2008, multidrug-resistant tuberculosis accounted for 5% of all tuberculosis cases, the highest percentage recorded to date. Even more frightening is the emergence of extensively drug-resistant tuberculosis that is resistant to all major TB drugs available. In the United States, seventy percent of the two million people who die from hospital-acquired infections were infected with strains resistant to at least one antibiotic. The CDC notes that \$1.1 billion dollars is spent annually on unnecessary antibiotic prescriptions for adult upper respiratory infections. Those billions of dollars could be spent on developing new antimicrobials, not needlessly encouraging antibiotic resistance.

Unfortunately, antibiotic resistance will never go away, owing to bacteria's incredible capacity to evolve and multiply. Bacteria have existed on Earth a thousand times longer than we have and can undergo 500,000 generations in the time it takes humans to undergo one.

These statements are not a call to panic, but rather a call to proactively confront antibiotic resistance. We can't eliminate antibiotic resistance but we *can* significantly reduce the rate and spread of antibiotic resistant pathogens.

While it is imperative that we use antibiotics prudently, prudent use alone is not enough. A multi-pronged approach that includes regulation, surveillance, research, and new antimicrobial discovery must be rigorously pursued in parallel.

Finally, while the use of antibiotics in agriculture is not the focus of today's hearing, it is an issue addressed in Chairwoman Slaughter's bill, the Preservation of Antibiotics in Medical Treatment Act, and it warrants more attention in this committee.

I look forward to learning about antibiotic resistance programs at the FDA and BARDA, and hearing concerns and recommendations from our versed witnesses.

Mr. PALLONE. Thank you, Ms. DeGette.

So that does conclude the opening statements by our members and we will turn to our first panel, who are already seated. I want to welcome you. On our first panel to our left, or to my left, I should say, is Dr. Janet Woodcock, who is director of the Center for Drug Evaluation and Research at the FDA, and next to her is Dr. Robin Robinson, who is director of Biomedical Advanced Research and Development Authority with the Department of Health and Human Services. You know the drill, 5-minute opening statements. They become part of the record, and you can submit additional written statements in writing for inclusion in the record after, if you like.

So I will begin with Dr. Woodcock. Thank you.

STATEMENTS OF JANET WOODCOCK, MD, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION; AND ROBIN ROBINSON, MD, DIRECTOR, BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY, DEPARTMENT OF HEALTH AND HUMAN SERVICES

STATEMENT OF JANET WOODCOCK

Dr. WOODCOCK. Mr. Chairman and members of the subcommittee, I am Janet Woodcock. I am the director of the Center for Drug Evaluation and Research at the FDA, and I thank you for the opportunity to testify on this important topic.

Maintaining access to lifesaving antibiotics and combating antimicrobial resistance are critically important to the FDA. As a rheumatologist, I can attest both to the power of these drugs as they save the lives of many of my immunocompromised patients and to the tragedy when they were really not enough to combat the infection and I lost young patients, some of the most difficult episodes of my professional career.

Antimicrobial therapy is really one of the triumphs of modern medicine. Louis Thomas, who is one of our distinguished American physicians, clinician and scientists, witnessed the dawn of the antibiotic era when he was a medical trainee, and he describes a transformation from helplessness in the face of almost certain death of a patient to intervention that could rapidly restore a patient to health. We can't go back to this helplessness, and I think that is what drives the concern about antibiotic resistance. These were truly wonder drugs at that time.

But what was not known at the time is that these medicines came with an expiration date. The use of antimicrobials, especially indiscriminate use, will affect the timing of that expiration date but every antibiotic will get to the end of its usefulness as the members have already said because the microbes have many strategies to elude our chemical attacks and so we must use our intelligence, our science and our technology to stay ahead of the microbes. We must use antimicrobials carefully to prolong their effectiveness but we must also have new interventions in the pipeline.

Over the last half century, biomedicine has relied upon the private sector to fill this pipeline fueled by government-supposed basic science. This arrangement has produced a vast array of active antimicrobials. However, over the last two decades a combination

of economic and scientific factors has decreased this productivity. The pipeline is diminished at a time when the need could not be greater.

I would like to provide some insight into the scientific problems that we face. Our success in developing antimicrobials means that most common infections are adequately treated with existing therapy. This change in the history of infections makes it more difficult to study new treatments. For critically ill individuals, though, time is of the essence in getting treatment and delays to obtain consent and to complete study enrollment are often not acceptable and limit enrollment of very ill patients into studies of new treatments and the historical widespread antibiotic use has resulted in a patchwork of resistance problems that have already been alluded to.

In the absence of rapid diagnostic tests for the identity and resistance patterns of the infecting organisms, doctors don't know what they are facing when they are treating an individual patient. These factors create the need for new scientific methods to study antimicrobial drugs. FDA has been working with the scientific community to develop these methods. This is an example of regulatory science, the kind that has been advanced by Dr. Peggy Hamburg, our FDA commissioner. FDA plans to publish additional guidance on these methods within the next 6 months to help establish new scientific standards for evaluation of antimicrobial drugs.

In closing, I would like to add a note of optimism to this picture. The filings for new studies of experimental antibiotics in people, which are called INDs, the first test of a new therapy in humans, has been in a steep decline since 1987, and every year we have seen fewer and fewer new compounds come into the clinic for testing, but in the last 3 years we have seen a reversal of this trend with a sharp upward move. We have seen more small companies and startups involved in the field and interest in medically important infectious conditions that lack good treatment. This may be good news for our patients. But to bring this into the hands of doctors, to bring these new innovations into the hands of doctors requires concerted effort on the part of academia, government and the private sector, and we hope to contribute to that. Thank you.

[The prepared statement of Dr. Woodcock follows:]



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

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

COMMITTEE ON ENERGY AND COMMERCE

SUBCOMMITTEE ON HEALTH

UNITED STATES HOUSE OF REPRESENTATIVES

HEARING ON

"PROMOTING THE DEVELOPMENT OF ANTIBIOTICS AND ENSURING
JUDICIOUS USE IN HUMANS"

JUNE 9, 2010

FOR RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, 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 a part of the Department of Health and Human Services (HHS). Thank you for the opportunity to discuss FDA's role in ensuring the ongoing availability of safe and effective antimicrobial drugs.

Preserving the effectiveness of current antimicrobials and encouraging the continued development of new ones is vital to protecting human and animal health against infectious microbes. A 2004 report from the Infectious Diseases Society of America (IDSA) noted that "About two million people acquire bacterial infections in U.S. hospitals each year, and 90,000 die as a result. About 70 percent of those infections are resistant to at least one drug." And the problem is not limited to hospitals. Clinicians practicing in every field of medicine, including veterinarians, encounter infections caused by resistant pathogens. The impact of resistant infections on affected patients and families is significant and tragic. As the IDSA also noted, "The trends toward increasing numbers of infection and increasing drug resistance show no sign of abating. Resistant pathogens lead to higher health care costs because they often require more expensive drugs and extended hospital stays."

As a nation, we must address this problem from many sides; the development of new antimicrobial drugs is only part of the solution. Microorganisms constantly evolve and are likely to grow resistant to any new drugs we develop. This poses a continuous challenge and demands long-term

solutions. We must be vigilant in protecting our vital antibiotic resources by reducing overuse and inappropriate use. We must support innovative research in microbiology, epidemiology and regulatory science and conduct surveillance to detect the emergence of new resistant strains at the earliest possible moment. Improved diagnostics will help curb overuse of antibiotics by allowing physicians to determine whether a patient has a bacterial infection and, if so, whether it is resistant to conventional antibiotics. New vaccines have the potential to reduce the incidence of disease, diminishing the need for antimicrobial treatment in the first place.

FDA is only one of many parties that need to be involved in a comprehensive solution. The main role of FDA in addressing this problem is to establish clear, predictable regulatory pathways and to expeditiously review applications for new antimicrobial drugs, diagnostics, and vaccines. FDA will continue to collaborate with our partners within the government, such as the Centers for Disease Control and Prevention (CDC), the U.S. Department of Agriculture (USDA), and the National Institutes of Health (NIH), and those outside the government.

In my testimony, I will provide background information on antimicrobials and antimicrobial resistance, and describe FDA's participation in the U.S. Interagency Task Force on Antimicrobial Resistance and our efforts to facilitate the development of new antimicrobial drugs, diagnostics, and vaccines.

BACKGROUND

Antimicrobial drugs are used to treat infections caused by microorganisms. The term "antimicrobial" refers broadly to drugs with activity against a variety of microorganisms

including bacteria, viruses, fungi, and parasites (such as malaria). The term “antibacterial” refers to drugs with activity against bacteria in particular. Another term commonly used to describe an antibacterial drug is “antibiotic.” This term refers to a natural compound produced by a fungus or another microorganism that kills bacteria that cause disease in humans or animals. Some antibacterial drugs are synthetic compounds; i.e., they are not produced by microorganisms. Though these do not meet the technical definition of antibiotics, they are referred to as antibiotics in common usage.

Antimicrobial resistance is the ability of bacteria or other microbes to evade the effects of a drug. Many factors contribute to the spread of antimicrobial resistance. In some cases, doctors prescribe antimicrobials too frequently or for infections against which they have no activity. Sometimes patients do not complete the prescribed course of an antimicrobial, making it more likely that surviving microbes will develop resistance. The use of subpotent or counterfeit antimicrobials also can contribute to resistance; counterfeit antimicrobials are a problem encountered particularly in the developing world. The injudicious use of important antimicrobial drugs in both human medicine and animal agriculture is of particular concern. Through international trade and travel, resistant microbes can spread quickly worldwide. As of today, antimicrobial resistance mechanisms have been reported for all known antibacterial drugs that are currently available for clinical use in human and veterinary medicine. In some cases, strains that are resistant to multiple antibacterial agents have been isolated.

Antimicrobial agents have been used in human and veterinary medicine for more than 70 years, with tremendous benefits to both human and animal health. Many infections that were fatal, or left

individuals with severe disabilities, are now treatable or preventable. However, because bacteria are so adept at becoming resistant to antibacterial drugs, it is essential that such drugs be used judiciously to delay the development of resistance.

U.S. INTERAGENCY TASK FORCE ON ANTIMICROBIAL RESISTANCE

The U.S. Interagency Task Force on Antimicrobial Resistance (Task Force) was created in 1999 to develop a national plan to combat antimicrobial resistance. FDA co-chairs the Task Force, along with the CDC and NIH.

The Task Force also includes the Agency for Healthcare Research and Quality (AHRQ), Centers for Medicare & Medicaid Services (CMS), the Health Resources and Services Administration (HRSA), USDA, the Department of Defense, the Department of Veterans Affairs, and the Environmental Protection Agency. In 2001, the U.S. Agency for International Development joined the Task Force to help address global antimicrobial resistance issues.

In 2001, the Task Force published the “Public Health Action Plan to Combat Antimicrobial Resistance” (Public Health Action Plan or the Action Plan). The Action Plan provides a blueprint for specific, coordinated federal actions to address the emerging threat of antimicrobial resistance. It reflects a broad-based consensus of federal agencies, with input from consultants from state and local health agencies, universities, professional societies, pharmaceutical companies, healthcare delivery organizations, agricultural producers, consumer groups, and other members of the public. The Action Plan has four major components: surveillance, prevention and control, research, and product

development. The Interagency Task Force has been working on a revised Action Plan. The revised Action Plan will provide more specific action items than the 2001 Action Plan and will include goal dates for completing many of the action items.

FACILITATING THE DEVELOPMENT OF NEW ANTIBACTERIAL PRODUCTS

No matter how assiduous our efforts to protect the effectiveness of existing antimicrobials, these drugs are likely to lose their effectiveness in the long run, and so new products must be developed. We understand that the pharmaceutical industry values predictability and clarity. FDA is working to provide scientifically sound guidance to industry on demonstrating the safety and effectiveness of new antibacterial drugs, particularly on indication-specific trial designs used to study a new drug. This work is a very important part of the Commissioner's Agency-wide regulatory science initiative.

The Challenges of Antimicrobial Development

The field of antibacterial drug development is currently facing challenges because of the lack of standardized data on the effect of treatment with antibacterial drugs in certain infections. In addition, there are challenges because of the complexities in designing informative, ethical, and scientifically sound clinical trials for studying antibacterial drugs.

In part we are victims of the remarkable historical success of antimicrobials. Because we have effective antibacterials, it is often unethical to compare a new candidate antibacterial to a placebo. Thus we often recommend comparing a new (or investigational) drug to a standard approved drug. But showing that an investigational drug performs about the same as a standard or control drug assumes that we know how the standard or control drug would perform in that trial. For many currently used antibacterials, although we are confident that they are effective, we may only have limited information to characterize their precise effects. Antibacterials initially became available during the 1930s and 1940s and they represented a tremendous advance in medicine. They were soon adopted as the standard of care in the treatment of a variety of infectious diseases. At that time, our methods for testing a drug's effectiveness were much less sophisticated. In some instances, antibacterial drug therapy was adopted as the standard of care without rigorous testing (for example, in a randomized, placebo-controlled trial) to assess the effect of antimicrobial drug therapy in a particular condition. Because of this, in many instances there is a dearth of information to quantitatively assess the effects of new antibacterial drugs in certain infections.

We also face other challenges in designing informative, ethical, and scientifically sound clinical trials for studying antibacterial drugs. For example, it can be difficult to enroll a patient with a serious acute bacterial infection because he or she may not be able to wait to be enrolled in a clinical trial to begin treatment when therapy must be urgently initiated. At the same time, if the patient receives other antibacterial drug therapy before enrolling in a trial, this may cloud the assessment of the effect of the new drug; if the patient does well it may be difficult to know whether the effect was due to the antibacterial drug that the patient received before enrollment in

the trial, the effect of the new drug, or the effect of both the prior therapy and the new drug. In addition, at the time a patient is enrolled in a trial, the cause of the patient's illness may not yet be established; results from culturing (growing) the bacteria may not be available at the time of enrollment. These are just some of the challenges faced in designing a clinical trial for antibacterial drugs.

FDA Guidance on Developing Antibacterial Drugs

As we noted, the current situation is challenging because there are unresolved scientific issues regarding appropriate clinical trial designs. FDA cannot overcome these scientific challenges alone, so we have been working to address these issues through guidance development, public workshops, and Advisory Committee meetings. A number of parties have contributed to these efforts, including professional societies such as the IDSA and others, and scientists from academia, industry, and government. Developing clear guidance will take some time, but the durability of our advice will depend upon the quality of the underlying science.

FDA has taken or is in the process of taking the following specific steps:

- We have been actively working to gather scientific information to inform the development of recommendations on designing informative, ethical, and feasible clinical trials.

- We have issued draft guidance documents, posted on the FDA website, concerning clinical trial designs for studying antibacterial drugs. These draft guidance documents cover various topics, including the following:
 - Non-inferiority clinical trial designs
 - Developing drugs for treating acute bacterial sinusitis
 - Developing drugs for treating acute bacterial otitis media
 - Developing drugs for treating acute bacterial exacerbation of chronic bronchitis in chronic obstructive pulmonary disease
 - Developing drugs for community-acquired bacterial pneumonia.

We are also working toward publishing additional draft guidance documents in the coming months for skin infections and hospital-acquired/ventilator-associated bacterial pneumonia. As part of the process for developing these guidance documents, FDA held a November 18, 2008, Advisory Committee meeting to discuss clinical trial designs for skin infections and a public workshop on March 31, 2009, and April 1, 2009, co-sponsored with IDSA, the American Thoracic Society, the American College of Chest Physicians, and the Society of Critical Care Medicine on hospital-acquired/ventilator-associated bacterial pneumonia.

From time to time FDA is asked whether groups outside of FDA can propose clinical trial designs that may include relatively unique or different strategies. We welcome scientifically sound proposals from groups outside of FDA regarding appropriate trial designs. FDA is always

willing to consider other study designs, if such designs will provide an informative and ethical means to assess the safety and efficacy of a drug.

Although the development of new antibacterial drugs is not the entire solution to the problem of antimicrobial resistance, it is a very important part of the solution to this important public health issue. We need new therapeutic options to treat the resistant bacteria that we currently face and we will need new therapeutic options in the future. FDA will continue to work with academia, industry, and others within the federal government to overcome the challenging scientific issues in this area. However, the work on guidance development and clinical trial designs will not alone be sufficient to overcome the challenges facing the field of antibacterial drug development. It will likely also take the development of incentives in order to stimulate the development of new antibacterial drugs so that we have new therapeutic options to treat the resistant pathogens that we currently face and the resistant pathogens that we will face in the years ahead.

IMPROVING DIAGNOSTICS FOR INFECTIOUS DISEASES

The development of new diagnostics can help combat antimicrobial resistance. Diagnostics can reduce the use of antimicrobials because they can help a physician decide if it is appropriate to stop antimicrobial use and which antimicrobial drug(s) are likely to be effective for treating a given patient's infection.

During the last three years, FDA has reviewed and cleared rapid tests for the detection of methicillin-resistant *Staphylococcus aureus* (MRSA) and identification of vancomycin-resistant *enterococci* (VRE) to aid in the prevention and control of MRSA infection or vancomycin-resistant infections in health care settings. We have also been working closely with CDC, the Biomedical Advanced Research and Development Authority (BARDA), and NIH to determine how to best assess the performance of diagnostics for antiviral resistant strains of the 2009 H1N1 influenza virus.

We have participated or will participate in three public workshops between November 2009 and July 2010 to solicit input related to diagnostic devices and antimicrobial resistance.

- On November 12-13, 2009, we co-sponsored a workshop along with IDSA entitled “FDA-IDSA Public Workshop: Advancing Clinical Development of Molecular and Other Diagnostic Tests for Respiratory Tract Infections.” This workshop was aimed at determining the barriers preventing the development of rapid tests that could be used to distinguish viral from bacterial respiratory tract infections.
- On June 7-8, 2010, we co-sponsored a workshop along with CDC and the National Institute of Allergy and Infectious Diseases (NIAID) within NIH that addressed 2009 Federal Tuberculosis Task Force recommendations regarding the development of new rapid methods for laboratory confirmation of tuberculosis and the identification of drug-resistant tuberculosis.
- On July 26-27, 2010, we are co-sponsoring a workshop along with IDSA and NIAID entitled “Issues in Antibacterial Resistance and Device and Drug Development.”

FACILITATING THE DEVELOPMENT OF NEW VACCINES

The development of new vaccines can also help combat antimicrobial resistance because the use of effective vaccines can reduce the need to use antimicrobials in the first place. Prevention of infections through the use of vaccines has effectively eliminated or markedly decreased the problem of resistance in organisms such as *Haemophilus influenzae* type b (virtually eliminated in the United States while still a problem in other parts of the world) and *Streptococcus pneumoniae*, also known as pneumococcus. FDA has also been very involved in facilitating the development of new vaccines to prevent diseases such as tuberculosis, malaria, and invasive *Staphylococcus aureus* infections.

We have taken the following specific actions to facilitate tuberculosis vaccine development:

- Developed an assay to measure the potency and assess the safety of new tuberculosis vaccines
- Characterized the safety and effectiveness of novel live attenuated tuberculosis vaccines
- Evaluated certain T-cells as potential correlates of protective immunity against tuberculosis

We have also worked with the World Health Organization and the Aeras Global Tuberculosis Foundation on tuberculosis vaccine issues.

To facilitate malaria vaccine development, we have:

- Developed a highly sensitive technique for measuring the number of malaria parasites in blood during vaccine studies
- Developed a tuberculosis-malaria co-infection model for evaluating the safety and effectiveness of co-administration of tuberculosis and malaria vaccines
- Identified excellent targets for genetic attenuation of a blood stage attenuated whole parasite vaccine

In addition to these specific actions related to development of vaccines for tuberculosis and malaria, we have also issued guidance, posted on the FDA website, concerning the development of vaccines to protect against global infectious diseases.

CONCLUSION

Antimicrobial resistance is a complex issue and addressing it will require creativity and persistence. But the dangers of widespread antimicrobial resistance are so severe that we simply must rise to the challenge. FDA will continue to work with federal, state, local, and foreign government officials, medical professionals, the regulated industry, and all of FDA's stakeholders, in developing sound strategies to address and advance both human and animal health. FDA looks forward to working with Congress on this important public health issue.

Thank you for the opportunity to testify today. I welcome your ideas and your questions.

Mr. PALLONE. Thank you, Dr. Woodcock.
Dr. Robinson.

STATEMENT OF ROBIN ROBINSON

Dr. ROBINSON. Good morning, Chairman Pallone, Ranking Member Shimkus, Chairmen Waxman and Dingell and other distinguished members of the subcommittee, I am Robin Robinson, director of Biomedical Advanced Research and Development Authority, known to most of you as BARDA, at HHS.

Antimicrobial resistance is a major concern to you, to the Nation and also to BARDA, and we appreciate the opportunity to talk to you about how we are going to move forward in combating this problem.

As has been stated, antimicrobials are our primary weapons in the fight against old and new infectious diseases. The discovery and development of antibiotics in the mid-20th century is among the greatest advances in the history of medicine and public health and they remain a mainstay in our treatment and use of medicine.

In addition to antibiotic resistance being a problem in community-acquired diseases, antibiotic resistance provides an additional concern to BARDA as resistance to current antimicrobials could be intentionally introduced by genetic manipulation and to otherwise susceptible bacteria including bioterrorism bacterial agents producing a biological superweapon that would render our stockpiles of antibiotics obsolete during an attack. Further, naturally occurring drug-resistant isolates of several biodefense pathogens including plague have been detected by environmental and clinical surveillance, making the availability of antibiotic-resistant bioterrorism pathogens even more feasible. Thus, the increasing prevalence of antimicrobial-resistant bacteria is not only a matter of concern for public health but of national security.

Antibiotic resistance is further exacerbated by the dearth of antibiotic candidates that are coming through the development pipeline with a little bit of glimmer coming from what Dr. Woodcock has just said. The consequences of the limited antibiotic development pipeline are obvious and seen every day among medical practitioners and public health officers with tragic outcomes for growing number of patients and using drugs that are becoming obsolete. The public health and biodefense repercussions of antibiotic resistance call for greater public-private partnerships between the federal government and industry to provide the necessary support, core clinical development and manufacturing services and incentives to make a robust development pipeline of new classes of antibiotics and other products.

Into this setting of escalating antibiotic resistance, what can BARDA do? BARDA was established by the Pandemic and All-Hazards Preparedness Act of 2006 to ensure the United States has sufficient supply of vaccine and drugs to respond to public health emergencies caused by pandemic influenza, chemical, biological, radiological and nuclear threats, and emerging infectious diseases. BARDA uniquely bridges a critical gap referred to as the Valley of Death in the public health, medical and biodefense infrastructure that is facilitating the advanced development and manufacturing acquisitions of medical countermeasures that have little or no com-


mercial markets by forcing public and private partnerships. In its short history, BARDA has taken a multi-pronged approach to pandemic influenza and biodefense medical countermeasure programs to stimulate drug and vaccine development and manufacturing capabilities.

Similarly, we have proposed that we move forward with this multi-pronged approach for antibiotic resistance. This approach and the authorities provided by the Pandemic and All-Hazards Preparedness Act would allow BARDA to develop new classes of antibiotics as well as other medicines including vaccines and diagnostics that are authorized under PAHPA for BARDA to address in this fight against antibiotic resistance.

So what would our strategy be for combating antibiotic resistance? First, to continue our development of new classes of broad-spectrum antimicrobials not only for biodefense but for public health. Secondly, vaccines for high-priority bacterial pathogens, and these vaccines would be, say, for Staph aureus that would combat MRSA. And lastly, point-of-care diagnostics for high-priority bacterial pathogens which would actually change the way that medicine could be practiced by actually having point-of-care diagnostics that a physician could provide the appropriate care for patients. Together these actually have a ripple effect not only on antimicrobial resistance but also in the pipeline for other drugs by using multi-utilization platform technologies and moving forward with these together we think that we can make a big difference going forward.

So I look forward to being able to answer questions for you in BARDA's section of the pie as we go forward. Thank you.

[The prepared statement of Dr. Robinson follows:]

	<p>Testimony Subcommittee on Health Committee on Energy and Commerce United States House of Representatives</p>
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BARDA Efforts to Counter Antimicrobial Resistance

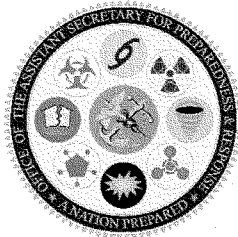
Statement of

Robin A. Robinson, Ph.D.

Deputy Assistant Secretary and BARDA Director

Office of the Assistant Secretary for Preparedness and Response

U.S. Department of Health and Human Services



For Release on Delivery
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Good morning Chairman Pallone, Ranking Member Shimkus and other distinguished Members of the Subcommittee. I am Dr. Robin Robinson, Director of the Biomedical Advanced Research and Development Authority (BARDA), an office within the Assistant Secretary for Preparedness and Response of the Department of Health and Human Services. Antimicrobial resistance is of major concern to this Congress, the Federal government, and the Nation. I appreciate the opportunity to talk with you today about BARDA's role in countering this growing problem.

Overview of Antimicrobial Resistance for Biodefense

Antimicrobials, a class of drugs that includes antibiotics, agents that kill or inhibit bacteria, and antivirals, which kill or inhibit viruses, are primary weapons in the fight against infectious disease. The discovery and development of antibiotics in the mid-twentieth century is among the greatest advances in the history of medicine and public health. Further, the advent of antiviral drugs provides new options for controlling previously untreatable viral infections. Antimicrobials are today, and will remain for the foreseeable future, an indispensable tool of medical practice and a cornerstone of public health, providing safe, simple, and effective treatments for serious communicable diseases.

Our ability to rely upon the availability of effective antimicrobial drugs is severely threatened. Ironically, this threat arises in large part from the use of the drugs themselves. Antimicrobial resistance occurs in microorganisms as a

manifestation of their ability to adapt to the environment. Under pressure by antimicrobials, bacteria have inevitably responded by evolving mechanisms for reducing their susceptibility to the drugs, resulting in the phenomenon known as antibiotic resistance.

As a result of this phenomenon, resistance to entire common antimicrobial classes, including β -lactams, quinolones, tetracyclines, glycopeptides and macrolides, is emerging rapidly and is already prevalent in health care and community settings. As widespread use of antibiotics has become common, the extent of the problem of antimicrobial resistance has grown.

Although antimicrobial resistance occurs naturally in microorganisms as a mechanism of adaptation to the environment, an additional concern is that the capability for resistance to current antimicrobials could be intentionally introduced by genetic manipulation into otherwise susceptible bacteria, including bioterror agents, producing a biological super-weapon that would render our stockpiles of antibiotics for treatment useless during a bacterial threat agent attack. Further, naturally occurring drug resistant isolates of several biodefense pathogens, including plague and meloidiosis, have been detected by environmental or clinical surveillance, suggesting that the obtainment of these strains by nefarious parties is technically feasible. Thus, the increasing prevalence of antimicrobial-resistant bacteria is a matter of concern for both public health and national security biodefense.

Although the phenomenon of resistance has been evolving since the first introduction of antibiotics, its impact has been mitigated because new antibiotics

have continually been developed and introduced to replace those that have lost effectiveness due to resistance, with a robust antimicrobial development pipeline maintained by the combined enterprise of academic, government and commercial interests. However, in the last 25 years, the number of new antimicrobials has steadily and dramatically decreased, reflecting in part an erosion of interest by the private sector in developing novel antimicrobial drugs.

The decrease in pharmaceutical company commitment to new antimicrobial development reflects an unfavorable assessment of the economics of the market for these products. The process of taking an antibiotic drug from discovery through development and testing to approval by the Food and Drug Administration (FDA) requires considerable time and financial resources. To justify this investment, drug companies look for a commensurate level of return in sales. However, the market dynamics of antibiotics are influenced by factors that make this outcome far from certain. The limited duration of most antibiotic regimens, leading to a cure, does not result in the continued sales that can be expected with drugs for chronic conditions. In addition, a new, effective antibiotic is likely to be initially reserved for severe infections that do not respond to other antibiotics, further limiting sales. Squeezed between the increasing cost of developing new drugs and uncertain prospects for a profitable market return, the commercial pharmaceutical industry has turned its attention to other drugs that command higher prices and are aimed at treating chronic conditions and diseases.

The consequences of the interrupted antibiotic pipeline are being felt by medical practitioners and observed in public health monitoring, with tragic outcomes for a growing number of individual patients. And the situation is likely to worsen before it improves. The lengthy drug development process means that new classes of drugs to supplement or replace current ones are still years away at best.

Faced with this looming crisis, a concerted effort is needed to provide short-term relief and long-term solutions to the problem of antibiotic resistance. The public health and biodefense interests of this effort call for the Federal government to take the lead in providing the necessary support and incentives to restore the commercial antibiotic pipeline and ensure the continuous availability of effective drugs to treat all bacteria that cause human disease.

BARDA's Efforts to Counter Antimicrobial Resistance

BARDA was established by the Pandemic and All-Hazards Preparedness Act of 2006 (PAHPA) to ensure that the United States has a sufficient supply of vaccines and drugs to respond to public health emergencies caused by pandemic influenza, emerging infectious diseases, and chemical, biological, radiological, and nuclear (CBRN) threats. BARDA addresses a critical niche in the public health and medical infrastructure to fill in the gap for enabling those types of medical countermeasures that the commercial markets have rejected based on current market forces. BARDA has designed and implemented programs that create partnerships between government and industry based on

support and incentives that induce the commercial enterprises to address public health and biodefense priorities.

Filling Market Gaps: BARDA as a Bridge over the “Valley of Death”

BARDA has taken a multi-faceted approach to its programs for stimulating drug and vaccine development. Pursuant to the Project BioShield Act of 2004, BARDA initially created markets for CBRN threats by committing to procure certain drugs and vaccines that would create a stockpile of treatments to be used in case of a bio-terror attack. From the experiences implementing Project BioShield, PAHPA was enacted in 2006 and authorized the award of up to half the contract amount for drugs and vaccines that reached critical “milestones” to be made before the projects have been completed. These contracts allow the government to effectively support advanced product development and ensure that companies have sufficient resources and incentives to take these products to licensure, thus bridging the “valley of death” between the funding of applied research and completed projects. Further, the development of antibiotics for the treatment of biological threat agent exposure concurrently increases the robustness of the developmental pipeline, as these candidate antibiotics also seek FDA approval for clinically relevant infectious diseases. BARDA has also provided support for the building of U.S.-based infrastructure for the development and manufacturing of vaccines, strengthening our overall capability for preparing for and responding to public health and bio-terror threats.

BARDA is currently applying these approaches and authorities to programs focused on pandemic influenza and high priority biodefense threats. BARDA is authorized to implement programs whose goal is the development of new antibiotics, as well as other tools for reducing infectious diseases, as part of an overall approach to the problem of antibiotic resistance. BARDA can conduct this work as a two-phase, coordinated strategy on countering antimicrobial resistance, comprised of 1) funding the acceleration of new antimicrobial product pipeline, and 2) supporting advanced development of vaccines for high-priority microbial pathogens.

Antimicrobial Strategy

For reasons discussed earlier, commercial market incentives are no longer driving a robust antibiotic development pipeline, necessitating government initiative to ensure that the system operates in the public interest. Our sister agencies within HHS are doing their part to stimulate activity at the discovery end of the pipeline, and to facilitate progress at the approval end. BARDA's role is to ensure progress through the critical development and manufacturing phases of the enterprise. Development of dual-purpose antibiotics useful for both bio-threats and public health pathogens is a key in the BARDA strategy.

BARDA's initial programs in antibiotic development have approached the development of new antibiotics from the perspective of filling gaps in our ability to respond to bacterial threat agents. Some of these threat agents do not currently have an FDA-approved treatment and some have the potential for becoming

resistant to current treatments through natural or intentional means. BARDA has supported the development of new formulation of existing antibiotics, including an inhalational (gentamicin) product for plague and tularemia. In the President's FY 2011 budget, BARDA requested funds to support advanced development of new classes of broad-spectrum antimicrobials that address critical gaps in antimicrobials against bio-threats and public health pathogens. In addition, on May 17, 2010 BARDA published a sources sought notification/ request for information regarding animal model development. The development of animal models is a key element in the successful development of medical countermeasures for CBRN threats, particularly since efficacy of products against most of these threats could never be verified using clinical studies. Of particular concern is the lack of animal models to demonstrate antibiotic efficacy for bacterial threats such as plague and tularemia. Lastly, BARDA supports efforts to develop appropriate animal models to support licensure of products, including antimicrobials, to address CBRN threats.

Further, BARDA has the authority to expand the scope of existing and new Broad Agency Announcement to include requests for submissions for advanced research and development for emerging infectious disease, including the development of novel therapies to treat multi-drug resistant microorganisms.

BARDA has the authority to develop new antibiotics for public health. BARDA can focus on antibiotic resistance as an emerging threat of imminent risk to the United States. Specific initiatives could also be designed to support commercial enterprises in the advanced development of new antibiotics that are

effective against bacteria that have become extensively resistant to current antibiotics and are an urgent concern for medical practitioners.

Vaccine Strategy

One of the ways BARDA can address the problem of antibiotic resistance is through the development of antibiotics; another way would be through the development of vaccines. Specifically, antibiotic resistance can be reduced by preventing disease, and thus decreasing the need for and usage of antibiotics. For this purpose, the availability and use of vaccines can play a key role. For bacterial pathogens that quickly develop resistance to each new antimicrobial, vaccines provide more reliable and long-term protection. Vaccines also have the potential, with widespread distribution, to drastically decrease treatment costs. The development and use of vaccines for bacterial diseases that cause high demand for antibiotics or have demonstrated a particular tendency to develop resistance can be a powerful complement in the strategy for preserving antibiotic effectiveness.

BARDA is authorized to play a role in supporting advanced research and development of vaccines against high-priority bacterial diseases. Since vaccines are specific for a single bacterial pathogen, as opposed to antibiotics, which may be effective against multiple pathogens in a class of organisms, these initiatives will be carefully targeted to bacteria that have already shown high levels of resistance to existing antimicrobials, such as *Staphylococcus aureus* (MRSA). In combination with BARDA's broad spectrum antibiotic development initiatives,

these vaccine programs will help maximize our ability to address the problem of antibiotic resistance and ensure the long-term security of this valuable medical resource well into the future.

Conclusion

In conclusion, BARDA's mission and capabilities make it well-suited to contribute to a national strategy to combat antimicrobial resistance. We view this effort as a key part of our current and future program direction, and are fully committed to addressing this important problem.

Again, I would like to thank the Subcommittee for the opportunity to testify, and look forward to your questions.

Mr. PALLONE. Thank you, Dr. Robinson, and we will move right to questions, and I will recognize myself initially.

I wanted to ask Dr. Woodcock a question. A couple of the witnesses on the second panel, which we haven't heard from but we have their testimony, they cite regulatory uncertainty as one of the factors contributing to why there are so few effective antibiotics on the market today and that this uncertainty compounds the other economic disincentives that confront companies considering investing in the development of new antibiotics. An example of this regulatory uncertainty, according to one of the witnesses, they cite the FDA's failure to finalize certain documents that would provide guidance to industry on how to satisfy FDA's requirements for pre-market clinical trials of specified antibiotics. Now, your testimony, Dr. Woodcock, describes some of the difficult questions and issues surrounding these clinical trials on new antibiotics and I recognize that the stakes here are high, but on the one hand you are faced with what we all recognize as a dangerous lack of new safe and effective antibiotics. On the other hand, FDA doesn't want to approve new antibiotics that not only may not work but could also contribute to the resistance problem. So formulating these guidelines is obviously not easy but I wanted you to tell some more about the difficulties you faced in developing and completing these guidelines, if you will.

Dr. WOODCOCK. Well, first of all, let me say that the regulatory path is pretty clear for an obviously superior treatment so if a treatment were developed that could beat other antibiotics or treat resistant therapy where no other antibiotic is effective, that regulatory path is very clear. The problem is for treatment areas where there is a lot of satisfactory therapy and those are typically the targets for commercial development because, as some of the members already alluded to, those are very widespread in the community, sinusitis and so forth. Where there is very effective therapy out there, it is difficult to tell whether a new treatment is actually equivalent to the existing treatments and we don't want to run the risk of successively approving more inferior treatments to the point where at some point we have approved therapies that aren't actually effective.

Mr. PALLONE. OK.

Dr. WOODCOCK. So we are developing new scientific methods to evaluate these conditions in a time where there is adequate antibiotic therapy out there and it is more difficult to do that. However, companies that wish to pursue other types of infections that are currently not very well treated, that is a clearer path but that is not as commercially desirable a path to get onto the market.

Mr. PALLONE. Now, what about the timelines? Can you tell us the anticipated timelines for completing the draft guidelines you listed in your testimony, and then what would companies or what should companies do now before they are completed? Can they rely on the draft guidances or wait until they are finalized?

Dr. WOODCOCK. Companies may come to the FDA and obtain advice on an individual basis, development plan basis, and that's what companies can do right now is talk to the FDA, but in an era, in a time of some scientific uncertainty, there is more risk to development, but I would reiterate that this is for these common infec-

tions, many of them that have currently satisfactory treatment. We do expect to move to finalize many of our guidances that we have published in draft. We are going to publish in the next 6 months several additional drafts of versions because there has been a great deal of scientific controversy about these evaluation methods and what methods would rely result in effective antibiotics being approved by the FDA, which is what we all, I think, want.

Mr. PALLONE. You are still talking about drafts, though. What about the final documents?

Dr. WOODCOCK. Yes, we will move to finalize these documents as rapidly as possible. We are moving to finalize some of the documents.

Mr. PALLONE. OK. I mean, it seems like these are very difficult scientific issues but at the same time it is important to get them right, but I just wanted to stress how important it is to resolve these issues and get these guidelines finalized as soon as possible. I know you are not giving me specific timeliness but it is really important to get it moving.

Dr. WOODCOCK. We agree with that, and we have recently entered into a collaboration to do what we call qualification work, which people might call validation work. We are looking at these new end points in clinical trials and see how they perform, and that is the kind of regulatory science work that really can move this ahead and provide everyone with the confidence that these new scientific methods are the right methods to test these new products and move them efficiently through the pipeline. So we agree but unfortunately there was some scientific work that had to be done to get these into final.

Mr. PALLONE. Thank you.

Mr. Shimkus.

Mr. SHIMKUS. Thank you, Mr. Chairman. I think I am going to follow your line, but first, Dr. Woodcock, the chairman had the benefit of receiving testimony from the second panel to read what they said to ask you questions. FDA submitted your testimony at 9:20 p.m. last night, or at least the minority staff got it at 9:20 p.m., which is way from the 48 hours. So we just want to raise that issue to ensure that we get timely submissions so we can do our due diligence on our side just as the chairman did, and that does help to have a heads-up of what the second panel is going to do.

Following into my questioning, I am going to follow this line of thought on the antibiotic development and regulatory uncertainty, which you were already alluding to. What we have heard is that there is not certainty or it is unclear the type of clinical trials that are needed, and when companies have invested a lot of capital in the trials, only then to be told that their clinical trials were insufficient, what can you do from a regulatory perspective to help clear up this regulatory uncertainty?

Dr. WOODCOCK. There is no doubt that predictability is one of the most important things for incentivizing commercial development in a specific indication area. So those who have to invest money need to know that if they dot all the i's and cross all the t's that they can get their—and the drug works and is safe they can get it across the finish line. We recognize that and we do everything possible to provide that predictability of development path. However, as

science changes, we have to—and the history of the diseases have changed based on the availability of all these other effective antibiotics, we have had to change the evaluation methods. That created a transition period that was very uncomfortable. We hope we are ending, reaching the end of that transition period so that we have new designs that are very clear and we have predictable development paths. But I will say I think that the time when companies seek to get sort of blockbuster antibiotics to treat otitis media or respiratory conditions and so forth and get those on the market, that is not exactly what you are talking about here, I think, in getting a new pipeline moving through. You are talking about getting new, effective antibiotics—

Mr. SHIMKUS. Right. My follow-up will be on the pipeline, so I mean, your analysis is correct. But it seems to me that what you are saying is, you don't need any additional authority to bring this certainty, you just need to make a decision for new antibiotic regime of what is then going to be considered a safe clinical trial, right? You have the authority to do this?

Dr. WOODCOCK. Yes, we have the authority. We need an evaluation method that we can rely upon, so if you test the antibiotic with that method you can reliably say that antibiotic works because that is what we are assuring the physicians and the patients is, you take this, this is an effective antibiotic.

Mr. SHIMKUS. Right. Then following up on what you mentioned before, is the pipeline there?

Dr. WOODCOCK. We are seeing—yes, the pipeline is diminished and has been for many years. What we are seeing in the very early stages of clinical development is a remarkable upturn. We can't—

Mr. SHIMKUS. And that is in your testimony. You talked about the decline, but then some new submissions by smaller companies in your testimony. Do you need to encourage more people to now get involved so that the pipeline is not there? Do you need any more additional authority?

Dr. WOODCOCK. I don't think it is FDA authority. Our role is to make sure these treatments are safe and effective and that there is a clear development path for these. It is clear, I think, to everyone that more incentives of some type or some type of encouragement of investors and companies and scientists and so forth to enter into this area is needed.

Mr. SHIMKUS. Thank you. Let me move quickly to Dr. Robinson. What is your role in fostering new antibiotic development?

Dr. ROBINSON. As I said in my testimony, we are responsible for antimicrobials for biotreats as part of our Project BioShield mandate but we are also responsible for emerging infectious disease as mandated by PAHPA, and we are reaching out further with dual-purpose antibiotics not only for plague, tularemia and so forth but also we will be going forward with community diseases including those that are gram-negative microorganisms. We see that the antibiotic resistance to TB really needs a very specific set of drugs and other approaches including that are non-antibiotics where a vaccine or vaccines may be applicable such as I mentioned the Staph aureus with MRSA but also with diagnostics as Dr. Frieden talked about and Dr. Fauci did, that one of the ways that we can help physicians immediately is by having point-of-care diagnostics

that allow them to make the proper diagnosis and then prescribe the correct drugs.

Mr. SHIMKUS. My time is expired. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. I just want to join with Mr. Shimkus's comments about the timeliness of the testimony. I understand it came in maybe a little earlier than what he said, but the bottom line is, we didn't get it until yesterday evening, and it is supposed to be 48 hours, and members, not that I am trying to bemoan us but we come in for votes at 6:30 and it is almost impossible to read the testimony the night before when you are just arriving here for votes, so I would just ask you and FDA, because I know he has pointed this out several times with FDA and Human and Health Services, we really need to get the testimony in in a timely fashion, otherwise we really can't formulate questions and really have an effective hearing. So I just wanted to mention that again.

The next is the gentlewoman from the Virgin Islands, Ms. Christensen.

Mrs. CHRISTENSEN. Thank you. I didn't expect to be coming up this quickly, and thank you both for being here and for your testimony again.

Dr. Woodcock, at the end of your testimony you gave us a little bit of good news, so to what do you attribute the increase or have you been able to attribute it to anything, the increase in the new investigations of antimicrobial drugs?

Dr. WOODCOCK. We are seeing this to some extent across the board in drug development, and I attribute it both to the new science that has identified a lot of new targets, genetics and so forth, so that is number one. Number two, there is a changing structure of the industry and there are a lot more players and different players who are getting into development and that is probably good news for diversity, and otherwise I don't think we know, but I think those are two of the major factors.

Mrs. CHRISTENSEN. Thank you.

Dr. Robinson, BARDA seems to have a fair amount of authority with regard to addressing this issue. Is there any further authority that BARDA would need to help us address this crisis?

Dr. ROBINSON. Thank you, ma'am. We have actually looked at this very carefully and we believe right now that with PAHPA that we do have the authority to move forward with this multi-pronged approach that will allow advanced development of all of these medical countermeasures to move forward. So I think right now we are OK.

Mrs. CHRISTENSEN. And I guess to both of you, one of the individuals on the second panel suggests that the federal government has not really been good or as strong a partner as they need to be so you don't need any other authority. Is funding the limitation?

Dr. ROBINSON. I will speak first on that. Because we have a number of different mandates and the funding for advanced development only came about in really the fiscal year 2007 budget, we certainly would need more resources to be able to address all the different priorities that we have including antibiotic resistance, yes.

Mrs. CHRISTENSEN. Dr. Woodcock.

Dr. WOODCOCK. We accomplish what we can with the resources that we have. There are needs for regulatory science that are quite

broad and this is one area. The research into the endpoints in trial design could help accelerate obviously getting guidances out in a timely manner and so forth. The President's budget for 2011 has a request for increasing regulatory science by the FDA commissioner. So I think we are limited to some extent because, like Dr. Robinson, by the large number of priorities that we deal with.

Mrs. CHRISTENSEN. And Dr. Woodcock, you also talked about some of the limitations in terms of the research limitations but the plan that the interagency task force put together has been in effect for 10 years. What percent or how much of that plan has been implemented and what other barriers might you have run into in implementing much of what you have set out?

Dr. WOODCOCK. Well, I believe that the plan will be updated and republished. There have been elements of that that have been accomplished but there is a plan to reupdate the plan and publish it with timelines for accomplishment of various activities which I think will help move that program along.

Mrs. CHRISTENSEN. Well, I didn't have a chance to look at the plan but has 10 percent, 30 percent of it been implemented over the 10 years?

Dr. WOODCOCK. I am sorry. I can't give you—we can get back to you on that.

Mrs. CHRISTENSEN. Thank you.

Mr. Chairman, I will yield back my time.

Mr. PALLONE. Thank you.

The gentleman from Kentucky, Mr. Whitfield.

Mr. WHITFIELD. Thank you all very much for your testimony. Dr. Woodcock, I would like to revisit this issue of lack of clarity and simply ask the question, in your view, is the criticism valid that the FDA does have a lack of clarity and it is unclear as to what type of clinical trials will be required for demonstrating safety and effectiveness? We hear a lot of criticism of the FDA in that regard, so in your view, is that criticism valid or not valid?

Dr. WOODCOCK. I would say it is valid to say that the scientific community has a lack of clarity on how to best evaluate new antibiotics and that is reflected in the fact that the FDA is struggling to get new guidances out there that reflect new evaluation methods that will be effective in today's environment. So had there been clarity in the scientific community, I think FDA could have effected this change very rapidly, but due to the lack of clarity we had to go through a great deal of effort to gain some type of consensus on how to do this.

Mr. WHITFIELD. It is seldom that the scientific community has very much clarity anyway, isn't it?

Dr. WOODCOCK. Well, we are no strangers to controversy in the area of how to evaluate medical products. However, this was a change that occurred between the 1980s and 2000, 1990 to 2000, a change that happened rapidly and it has been very difficult to get a new state of clarity about how to do this antibiotic development.

Mr. WHITFIELD. Would you explain the Orphan Drug Act for me, please? And also it is my understanding that there are grants available under the Orphan Drug Act and the amount of money involved in those grants and it is also my understanding that you all were required in the 2007 act to have a public hearing, which I

think occurred in April maybe of this past year and what the results of that were and what you are doing to follow up on those recommendations?

Dr. WOODCOCK. The Orphan Drug Act allows for incentives, grants as well as exclusivity for products to get onto the market for products that are intended to treat populations smaller than 200,000 individuals in the United States.

Mr. WHITFIELD. Smaller than 200,000?

Dr. WOODCOCK. Yes, and so this has been a wildly successful program in incentivizing the development of drugs for small populations, and I think there is agreement across the board about that, which is very rare to get such agreement. So it has been a very successful program. Its applicability to antibiotics is limited to the extent that where the population is often larger than that of treated patients for the given indication but for small indications where there is fewer than 200,000 people that would present with that condition in the United States, then the orphan provisions are germane.

Mr. WHITFIELD. What is the dollar value of the grants that would be available under that program?

Dr. WOODCOCK. I don't know. We would have to get back to you on that. I think they vary, but one of the more valuable issues is the orphan exclusivity that is given to the product if it successfully gets on the market.

Mr. WHITFIELD. And how did that April hearing go or forum go?

Dr. WOODCOCK. Again, I would have to get back to you on that. I don't have the details of that.

Mr. WHITFIELD. OK. You were not there?

Dr. WOODCOCK. No.

Mr. WHITFIELD. I yield back the balance of my time.

Mr. PALLONE. Thank you.

Next is the gentleman from Maryland, Mr. Sarbanes. He has no questions.

We will go to Mr. Burgess, who actually has 8 minutes.

Mr. BURGESS. Thank you, Mr. Chairman.

And again, thank you both for being here, very informative discussion.

Dr. Woodcock, you made the statement during your testimony that the microbes have strategies. I guess that begs the question, do we—because it does seem like we have got a problem both with the product in the pipeline and perhaps the pipeline itself may be old and rusty and full of obstacles. So are we—how do you feel about how we are updating that infrastructure to get this job done?

Dr. WOODCOCK. Well, obviously we all agree that prudent uses and preventing infection is one of the mainstays of this but we also must have a pipeline and I feel that many of the issues covered by the members already such as the short-term use of antibiotics, the regulatory or scientific difficulties nowadays in the development path, until recently probably the lack of new targets because the antibiotics were often all focused on the same microbial targets and now there is a broader range of targets. So I think there is room for optimism. However, I do believe that more commercial interest in this field needs to occur to really get the pipeline robust.

Mr. BURGESS. Well, Dr. Robinson mentioned two issues, but let us stay with you, Dr. Woodcock, because the FDA plays a role here in becoming available. One was the point-of-care diagnostics and the other were the vaccines where you go from a broader spectrum now down to a narrower spectrum but if you have fewer bugs that are actually able to become resistant, then you'll reduce the likelihood of resistance. So how is the FDA doing as far as getting those two tools that BARDA is developing, how is the FDA doing it getting those into the hands of clinicians?

Dr. WOODCOCK. The FDA has approved several point-of-care diagnostics recently, several diagnostics for MRSA. However, they have to go through an additional step of the CLIA process to be approved for use in the practitioner's office, but I think this is very promising as far as that rapid microbial testing can be developed.

Mr. BURGESS. But this is a problem, though, I mean, with CLIA, I wasn't here but CLIA meant that we couldn't even make a microscopic slide and look at it under the microscope for clinically easily recognizable pathogens because I was not licensed to do that. So what happened, of course, I would do it and not charge for it and not tell anyone I was doing it say my clinical acumen tells me this is X even though I have identified it under the microscope. What a waste of time. Are we trying to improve that part as well or is that beyond the scope of the FDA?

Dr. WOODCOCK. CLIA, as you know, is administered by CMS. However, this particular issue is simply to show that the diagnostic is effective in use in the hands of the practitioner and then it can be used in the hands of the practitioner. So it is simply a demonstration that practitioners can use such a diagnostic like the rapid strep test or whatever in the setting of an office.

Mr. BURGESS. I didn't mean to get off on that. I still have a great deal of emotional difficulty with the affronts to my clinical judgment from CLIA.

Let me ask you this. The new molecular entities approved by the FDA in the last decade, I think for the last hearing my staff had prepared for me a list of 10 new molecular entities. Does that sound about right?

Dr. WOODCOCK. That sounds about right.

Mr. BURGESS. Is that OK, one a year for the last decade, or now over the last decade?

Dr. WOODCOCK. Well, this reflects the slide in the pipeline since 1987 where the new INDs have progressively decreased every year since 1987 until recently. So it takes about 5 or 6 years in the clinic from first in human studies to see therapies coming out and being available to doctors.

Mr. BURGESS. Do you know, are there any applications that have been filed with the FDA to get approval for new diagnostics for bacterial infections? Do you know if you have approved any? Has the FDA approved any of those new diagnostics?

Dr. WOODCOCK. As I said, we have approved several over the last several years, yes, for rapid diagnostics.

Mr. BURGESS. You know, Mr. Waxman, who unfortunately is not here, asked unanimous consent to insert into the record a letter from Advanced Life Sciences, and I asked to look at it just because I wanted to see what he was putting into the record, but it is very

interesting. I mean, here is a company that has developed a single does or once-a-day oral therapy for methicillin-resistant *Staph aureus* and we talked about patient compliance. You tell a patient they have got to take something every 4 hours, guess what? They aren't going to do it. They will do what I did, which I don't recommend, which is you take the antibiotic to toxicity and then back off, and if you feel better, you don't take it anymore. That is what patients do. That is real-world stuff. So if you give them one pill a day, they are much more likely to comply with the regimen. So this actually sounds like something that might be very useful. We have got a pathogen that is a series pathogen for community-acquired pneumonia and it is multiply-resistant *Staph aureus*, a once-a-day therapy, and here the company has done all the stuff they needed to do to get it going and then the rules changed on them in the middle of the application and they had to go back to square one. This is a small company. This is not one of the big houses that now we say won't participate, and this is exactly the type of company we want involved in this and they are apparently coming to Chairman Waxman with the information that they can't—you know, they had to start all over again, significant cost to them because they are a small startup company. What do you say to that? Why are we putting these kind of obstacles out there?

Dr. WOODCOCK. Well, it is a very difficult situation when the scientific needs for scientific evaluation changed during a development program, and it is very difficult for small companies. We try to avoid that as much as we can but the science may chance in advance—

Mr. BURGESS. And I recognize that, but can you not, and the advisory panels, can you not build in the flexibility as you are going through these? I mean, you changed the endpoints after the new drug application has been submitted. They have already invested considerable time and money. They could walk away from the project. Fortunately, they have not because I think this is a product that ultimately will benefit patients. But, really, it seems like there has got to be more flexibility. These are relatively unique situations that develop but more flexibility at the regulatory side to deal with just these types of problems. I mean, suffice it to say if Sir Alexander Fleming had come up against this, he might have never had a statue of himself erected by the bullfighters in Spain because he wouldn't have been able to get penicillin cleared through your agency.

Dr. WOODCOCK. We understand. I can't discuss any specific case but we certainly try to build in flexibility and we recognize that changing—and that is actually built into our procedures. We try not to change our advisory requirements during a development program if at all possible.

Mr. BURGESS. I don't mean to interrupt, but my time is going to run out, and they are really tough on me with the gavel here, but do you really feel like you are getting a clear regulatory pathway so everyone can know the rules and then if we do change the rules in the middle, we at least have some certainty for these companies that at some point the regulations will cease and they will get either a yes or no on their product? Because that is after all what they need to hear.

Dr. WOODCOCK. We recognize how important that is to stimulate and sustain development in any indication area. We definitely recognize that predictability is key.

Mr. BURGESS. Thank you, Mr. Chairman.

Mr. PALLONE. Since you suggested we should be tough, I guess we will have to be.

Mr. BURGESS. I will give you back Mr. Waxman's submission for the record.

Mr. PALLONE. Thank you.

Next is the gentleman from Texas, Mr. Green.

Mr. GREEN. Thank you, Mr. Chairman. And I have never thought you wielded a heavy gavel. I would ask permission to submit my opening statement for the record, Mr. Chairman.

[The prepared statement of Mr. Green follows:]

**Statement of Congressman Gene Green
House Energy and Commerce Committee
Subcommittee on Health
“Promoting the Development of Antibiotics and Ensuring Judicious Use in Humans”
June 9, 2010**

Mr. Chairman, thank you for holding this hearing on promoting the development of new antibiotics and ensuring appropriate use of antibiotics in humans.

Over the years individuals have become accustomed to receiving or even requesting a prescription for antibiotics when they see a doctor if they have a cold or other illness.

In many instances, antibiotics are not the appropriate course of treatment for a common cold. Antibiotics should only be used for bacterial infections, but because of their wide availability, they are often over-prescribed or over requested by patients.

The overuse and misuse of antibiotics has led to increasing levels of antibiotic resistance, which as we know from a hearing we had a few weeks ago, the spread of these new antibiotic-resistant infections has serious public health consequences for our citizens.

Antibiotic-resistant bacteria may keep people sicker and for longer time, sometimes rendering them unable to recover at all. Our children, elderly, and those with weakened immune systems are especially vulnerable.

I also hope that we can invest in research and encourage the production and development of new anti-infective drugs.

Pharmaceutical companies are often hesitant to invest in the development of new antibiotics because the return on their investment is very small. In hearing the testimony today, I would like to see if we can encourage these companies to invest in the development of these medications.

Thank you again, Mr. Chairman, for holding this hearing and I look forward from hearing from our witnesses today on measures we can take to ensure and encourage appropriate use and prescription of antibiotics.

Mr. PALLONE. Without objection, so ordered. All members may submit their statements without even making the request actually.

Mr. GREEN. Thank you, Mr. Chairman.

Dr. Robinson, you explained some of the challenges that hinder antibiotic development and I would like to ask about a potential solution to encouraging companies to work on developing antibiotics, advance market commitment. I understand the way the strategy works. The government contracts with a company to buy a certain number of doses of a product at a specific price. This gives the company a certain level of assurance that there will be a market for their product on an agreed-upon price. This is similar to what you do for other certain countermeasures which traditional market forces doesn't work, smallpox or anthrax vaccines. Do you think this approach, should we consider antibiotics for this approach?

Dr. ROBINSON. Well, certainly because we have antibiotics as part of our mainstay against biotreats, I would have to say this is something we would have to consider going forward. For public health reasons, it should be openly discussed with the medical communities and also considered as one of our possibilities to incentivize going forward, yes.

Mr. GREEN. And one of my concerns about stockpiling is, we also have shelf life to obviously antibiotics and any other medication, and that is something you dealt with, though, with the smallpox and anthrax vaccines, I assume?

Dr. ROBINSON. Certainly with the therapeutics we have a shelf life extension program that the FDA has so admirably held for a number of years now, and I think that we can utilize that going forward with new antibiotics that would come into the stockpile.

Mr. GREEN. So you don't see any logistical challenges? I mean, you have already addressed some of the challenges of other medications. You could do the same with antibiotics?

Dr. ROBINSON. That is correct. It would be a policy issue at this point.

Mr. GREEN. Dr. Woodcock, one of the suggestions for creating incentives for antibiotic is expand the concept of tropical disease priority review vouchers established under the FDA Amendments Act. Such a voucher would entitle the holder to get a drug reviewed with a target completion time of 6 months. Under such an approach, FDA would give a company a priority review voucher as a reward for developing a qualified infectious disease product. The company could use the voucher for a drug of its choice or could sell it to another company. Dr. Woodcock, could you tell us how the existing tropical disease program has worked from the FDA's perspective? Does it seem like a workable approach for important new antibiotics, and what are the tradeoffs in terms of FDA review of other drugs if we have that 6-month provision in there?

Dr. WOODCOCK. Well, I don't think that there has been enough activity so far under the tropical disease provisions to provide an assessment but we can get back to you on exactly what has happened but, you know, I don't think there has been enough action there to provide an assessment.

As far as the tradeoffs, I think if you wanted to think of this more broadly and apply it more broadly, what this does would decrease the FDA review time from 10 months to 6 months for any

given product and could be applied to any product, and most likely a company would apply it to a product that would normally be for a chronic disease, widespread treatment, right, and might be used to treat tens of millions of Americans, and this would mean that FDA would have to review that much faster than ordinary because the voucher had been applied to that. So I think there are some limitations on that approach because when we get a lot of priority reviews, especially where we are reviewing a drug that tens of millions of Americans might be exposed to it and it may be for chronic but not really important condition, we have to be really sure of the safety of that drug. We have to do a very, very careful review, and if we had large numbers of short reviews for products like that, I think that would be problematic for our review structure.

Mr. GREEN. I know one of the concerns I have is, I have a district in Houston, Texas, and we are seeing many more tropical diseases, for example, that are coming into our country, whether it is global warming or what, but if there is a problem, it is going to be in Houston and Dallas and San Antonio and shortly in Chicago and other places. So that is why I think some of that is really needed to respond to in our own country, much less what is happening in other parts of the world.

Mr. Chairman, I actually gave you 6 seconds back. Thank you.

Mr. PALLONE. Thank you, Mr. Green.

The gentleman from Georgia, Mr. Gingrey.

Mr. GINGREY. Mr. Chairman, I want to read an excerpt into the hearing record from the Administration's own interagency task force on antimicrobial resistance. The task force wrote a public health action plan in 2008 that reads in part, "Existing market incentives and regulatory processes may be insufficient to stimulate the development of certain priority antimicrobial-resistant products while fostering their appropriate use. The goal is to investigate and act upon potential approaches for stimulating and speeding the entire antimicrobial-resistant product development process from drug discovery through licensing. Drs. Woodcock and Robinson, do you agree with that statement?"

Dr. WOODCOCK. It is critically important if you want to increase the activity in a given sector to provide adequate incentives and discovery is important because we need new targets. We need antimicrobials that are going against a broader range of activities of the microbes and development is important because it requires a great deal of investment to get a product through and there has to be seen some type of return on investment in order to get robust investment in that sector. So I think those things are extremely important and we have to think them through very carefully.

Mr. GINGREY. So you do agree.

Dr. Robinson, would you agree also as well?

Dr. ROBINSON. Yes, I would agree, absolutely, because advanced development is the area that BARDA plays that when Dr. Fauci was here, he was talking about discovery and early development and then the market over here. Well, that is what BARDA does. It makes sure it can get from early development all the way to the market.

Mr. GINGREY. Doctors, can you tell the committee what organizations actually co-chair this task force, the Administration's inter-agency task force on antimicrobial resistance?

Dr. WOODCOCK. I believe CDC, NIH and FDA.

Mr. GINGREY. I think you are right, Dr. Woodcock.

Dr. Robinson, you won't have to second-guess her. That is exactly right.

If your 2008 report is true, and it is a report that is co-chaired by CDC, HHS and FDA, as Dr. Woodcock knew and reported, if the report is true, and we do need to look outside current market and regulatory incentives to stimulate antibiotic development, what other incentives might we as a government provide? As an example, would liability protection in certain circumstances help support greater innovation? Dr. Robinson?

Dr. ROBINSON. With the liability relief that has been provided previously by Congress with the PREP Act, we have actually applied that with declarations during events that would include some of the antibiotics, and what we were told by industry was that that was very helpful and that some form of liability relief is important.

Mr. GINGREY. Sort of like in the vaccine production when we really need something to combat H1N1.

Dr. Woodcock.

Dr. WOODCOCK. Well, I think I don't have further opinion on the liability issue. Obviously any type of incentive is important and I think any incentives have to be considered in light of whether or not you want to have restrictions at the other end because one of the goals here would be to restrict the use or moderate the use or make sure the use is very prudent of the intervention to preserve its effect as long as possible, and that is—we have our current problems with the pipeline but if we contemplated a pipeline that would end up with antimicrobials that would only be used in niche situations where they were really needed, that would be even a further disincentive, but you have to think about that as a goal to preserve the effect of that for a long time to protect the population and what kind of incentives would stimulate that.

Mr. GINGREY. Well, certainly I have an opinion on that and a very definitive opinion in regard to the development of the vaccines. I felt like liability protection was absolutely essential for us to move forward in that direction.

Now, this last question real quickly, and I don't have an opinion on this. I am just very curious to know what you think about it, though. Do our current antitrust laws allow companies to work together to create and expedite new antibiotics? And if not, if those laws don't allow that, would an easing of the law prove beneficial, do you think?

Dr. ROBINSON. Sir, I will give you an example where we actually have used the authority given to BARDA for antitrust exemption, and we actually used with the development of the H5N1 and the H1N1 vaccine. It was very important that we have that. Certainly in our case, we could actually use that and actually provide our sister agencies to be there also, which we normally do.

Mr. GINGREY. Dr. Woodcock.

Dr. WOODCOCK. I have worked in public-private partnerships where we have gotten companies together to advance general soci-

etal goals and they have had to be extremely lawyer-intensive on the antitrust issues, so there is no doubt, I think, that it is a barrier to working together to advance broader goals.

Mr. GINGREY. Great. I think that is very helpful and I appreciate your response.

Mr. Chairman, you are pretty generous with that gavel. I will yield back 1 minute late.

Mr. PALLONE. Thank you.

Mr. Murphy of Pennsylvania.

Mr. MURPHY OF PENNSYLVANIA. Thank you, Mr. Chairman. I have been sitting here going over some of the FDA Web sites on this information. I know you have quite a public campaign, preserving our treasure, knowing how antibiotics work, et cetera. Have you measured the effectiveness of your campaigns in terms of working with the public in reducing their demands on physicians for antibiotics when it is not the appropriate medication?

Dr. WOODCOCK. I believe especially the CDC's recent campaign—

Mr. MURPHY OF PENNSYLVANIA. The CDC's, yes, CDC and FDA on the same sites, yes.

Dr. WOODCOCK [continuing]. Did have an impact that was measured on reducing antibiotic use in sort of inappropriate conditions, yes.

Mr. MURPHY OF PENNSYLVANIA. Is that something we are going to see continued and expanded? I mean, we have talking a good bit about that today in terms of the kind of comments you have made and members have made. I am just wondering if that is something that you see that we should continue to fund and push for a widespread public education on that, and I might add, including the things you heard in my earlier commentary about the need for prevention, and I am amazed sometimes, I will go into hospitals where you can't walk down the hall without someone being fairly militant and making you gown and glove and wash your hands, which is good. I have heard of other dynamic things. To get in the ICU at University of Miami Medical Center, you don't push a button, there's not a sensitive sensor. To get in the door, you have to put your hand under an alcohol dispenser, and then when it squirts in your hands, the doors open. That is a very clever idea. Or I have also heard of systems where the doctors wear little monitors or anybody, and when they enter a room if they not washed their hands, a little mini alarm goes off and says "Wash your hands, please," and then the chairman hits them with the gavel. Not true, sir. I am continuing the theme here. But I am just wondering about public education campaigns that we do to reduce the need there.

Dr. WOODCOCK. I believe that is extraordinarily important. No matter what we do to the pipeline, and I think the last 20 years have shown us that, if there is indiscriminate use, then that will accelerate the development of resistance and our pipeline will continue to have trouble getting ahead of that. The recent scientific emerging understanding about infection control and how effective these simple measures actually can be if they are rigorously followed I think has startled a lot of people and provides a tremendous opportunity for improving quality in health care and decreasing infections, as you said, but each of those I believe needs contin-

ued pressure and education and interest to perpetuate them and they will go a long way toward dealing with this problem.

Mr. MURPHY OF PENNSYLVANIA. Well, I want to encourage all of you. I know when some of the recent flu outbreaks came out, you couldn't get into a bus stop without seeing a sign somewhere, and that was excellent. I thought it was very helpful.

The second thing I wanted to ask about has to do with since when people are sick they want to do something, and so there are a number of over-the-counter products, and either of you can answer this too, in terms of what we should be doing to help promote those for symptom assistance as opposed to the false promise of antibiotics for virus, other things we should be doing to encourage more OTC products, over-the-counter products instead. Is that in any of your purview that you want to comment on that?

Dr. WOODCOCK. FDA regulates the over-the-counter drugs, and we certainly—there is certainly a huge array of symptomatic control available for common viral illnesses that people suffer and also there are many other simple measures. So I think much of this is public education about the availability of straightforward symptomatic control for viral illnesses.

Mr. MURPHY OF PENNSYLVANIA. Do you have anything to add on that, Dr. Robinson.

Dr. ROBINSON. I would just concur with that also. I mean, we have had a number of different sponsors come to us for support looking at very simplistic type of products like that.

Mr. MURPHY OF PENNSYLVANIA. I might add to my editorial comments. I know that cuts to allow people to have their health care plan use their monies to pay for over-the-counter drugs, I don't like that idea because here we are talking about a massive amount of money we have to put into research and prescribing costs for antibiotics that we are building resistance to when we should be encouraging people to use other symptom remedies for that which are much less expensive and of course appropriate for those things too, so I hope those are things that we will restore in the future and I want to thank you both for your testimony. It is good to read this.

I yield back, Mr. Chairman.

Mr. PALLONE. Thank you.

The gentlewoman from Tennessee, Ms. Blackburn.

Mrs. BLACKBURN. Thank you, Mr. Chairman.

I am going to be very brief. I just want to go back to what Chairman Pallone was talking about at the very first, and I touched on it in my opening statement, our concern with the uncertainty that seems to exist at the FDA. And in my district in Tennessee, we have some wonderful groups that are doing tremendous amounts of research in biotherapies and in new therapies that are coming along the chain. We hear repeatedly about concern with the uncertainty from the FDA. You mentioned, Dr. Woodcock, that there has been a decline in the pipeline since 1987 and then we have also touched on the disincentives that are there. Dr. Robinson mentioned some of those. And I think that it is important that we realize those disincentives and the uncertainty at the FDA have a direct effect on what is there in that pipeline, and you keep saying, you have mentioned several times you have the authority that is necessary, Dr. Woodcock, to finalize these documents and provide

some certainty on that pathway, and I would just highlight with you that we think that that is important to do. If you have the authority, maybe you have too much authority. Maybe we need to pull some of that back and oversight and be just a little more direct and participatory in trying to help define that, but I would just highlight with you that it is of concern to us. We appreciate the work that you are doing but we do have great concerns about the uncertainty and the disincentives and the decline in the pipeline, and with that I will yield back.

Mr. PALLONE. Thank you. And let me thank both of you for being here today. It was obviously very helpful to us in this sort of three-pronged effort here with three hearings to get to the bottom of some of these problems and what is happening. Thank you.

I will ask the second panel to come forward at this time. Let me introduce—well, first of all, welcome, and let me introduce the second panel. Starting to my left is Dr. Brad Spellberg, who is associate professor of medicine, the David Geffen School of Medicine at UCLA and a member of the Infectious Diseases Society of America Antimicrobial Availability Task Force. Second is Dr. Sandra Fryhofer, who is from the Council on Science and Public Health at the American Medical Association. Then we have Dr. John Bradley, who is speaking on behalf of the American Academy of Pediatrics. He is the chief of the Division of Infectious Diseases. He is with the Department of Pediatrics at the University of California School of Medicine, clinical director of the Division of Infectious Diseases and he is also at Rady Children's Hospital in San Diego. That is a long list there. And then we have Dr. Barry Eisenstein, who is senior vice president of scientific affairs for Cubist Pharmaceuticals. I have to ask you, I keep looking at this Cubist, is that just the drug that you—what does the Cubist refer to?

Dr. EISENSTEIN. We believe that medicine and science involved in drug development is both an art and a science.

Mr. PALLONE. Oh, so it is reference to a cube, in other words. OK. Thank you.

And last is Dr. Jeffrey Levi, who is executive director of the Trust for America's Health. He has testified many times before the committee, and I hope that we did not contribute to your leg being broken or whatever happened to you.

Mr. LEVI. No.

Mr. PALLONE. Thank you for being here today.

So you know we have 5-minute opening statements that become part of the record and then we may ask you, or you may submit additional written statements if you like, and we will start with Dr. Spellberg.

Dr. SPELLBERG. Thank you. Could we cue up the slides, please?

Mr. PALLONE. Oh.

Dr. SPELLBERG. Great.

Mr. PALLONE. It is up there.

STATEMENTS OF BRAD SPELLBERG, MD, FIDSA, ASSOCIATE PROFESSOR OF MEDICINE, DAVID GEFEN SCHOOL OF MEDICINE AT UCLA, MEMBER, INFECTIOUS DISEASES SOCIETY OF AMERICA ANTIMICROBIAL AVAILABILITY TASK FORCE; SANDRA FRYHOFER, MD, COUNCIL ON SCIENCE AND PUBLIC HEALTH, AMERICAN MEDICAL ASSOCIATION; JOHN S. BRADLEY, MD, ON BEHALF OF AMERICAN ACADEMY OF PEDIATRICS, CHIEF, DIVISION OF INFECTIOUS DISEASES, DEPARTMENT OF PEDIATRICS, UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE, CLINICAL DIRECTOR, DIVISION OF INFECTIOUS DISEASES, RADY CHILDREN'S HOSPITAL, SAN DIEGO; BARRY EISENSTEIN, MD, FACP, FIDSA, SENIOR VICE PRESIDENT, SCIENTIFIC AFFAIRS, CUBIST PHARMACEUTICALS; AND JEFFREY LEVI, PHD, EXECUTIVE DIRECTOR, TRUST FOR AMERICA'S HEALTH

STATEMENT OF BRAD SPELLBERG

Dr. SPELLBERG. Thank you very much, Mr. Chairman. My name is Dr. Brad Spellberg. I am an infectious disease specialist, as you said, at the UCLA School of Medicine and Harbor UCLA Medical Center. I am also the author of "Rising Plague," which is a book about the antibiotic crisis, and it is my honor today to be here representing the Infectious Diseases Society of America, which is an organization of more than 9,000 physicians, pharmacists and scientists that all work in infectious diseases and microbiology.

In 2004, the IDSA released the "Bad Bugs, No Drugs" white paper to inform the public and Congress about the looming antibiotic crisis and more recently just in the last couple of months, the IDSA has released the 10 by 20 initiative, which calls for the development of 10 new critically needed antibiotics by the year 2020. And the reason why we are here today and the reason why IDSA has released "Bad Bugs, No Drugs" and the 10 by 20 initiative is because we are here to advocate for our patients that are dying of infections and we are running out of drugs to throw at them.

[Slide.]

This graph shows the number of new systemic antibacterial agents approved by the FDA for a 5-year period. The conclusion from this graph is inescapable: antibiotic development is dying. And at the same time, we are witnessing skyrocketing incidences of multidrug-resistant bacterial infections of a variety of types, some of which are shown on this graph, but there are many other types as well. This of course creates a critical need for new antibiotics to be developed right at the time when new antibiotics are not being developed, and these infections hit hospitalized patients, infirm patients, sick patients, the elderly, but they also hit the healthiest and strongest among us. In particular our soldiers in Iraq and Afghanistan have been devastated by a wide variety of multidrug-resistant bacterial infections. And this highlights a central point, which is that everyone is at risk for these infections including healthy people in communities, and as shown on this slide are examples of real patients who were healthy in communities and have been killed or maimed by multidrug-resistant bacterial infections. Everyone is at risk. The collective toll of these infections in terms of number of people infected, number killed and the multibil-

lions of dollars per year that these infections cost our health care system is absolutely staggering.

We have to start thinking of antibiotics as a precious limited resource in the same way that we view forestry, fisheries and energy policy. We need to both conserve and restore this precious resource and currently we do neither. We overuse and waste our antibiotics in both humans and animals, and the antibiotic resource is not being restored, because as we have heard, both there is an economic disincentive because antibiotics are not economically competitive with other drugs and there are regulatory barriers that prevent companies from understanding how to do clinical trials to get antibiotics approved.

So we need a multi-pronged approach to solving these problems, as we have heard. We need a multi-pronged approach to promoting antibiotic conservation. We need much better, more effective and widespread antibiotic stewardship programs to be used all over the country and frankly throughout the world. We need funding to be made available to CDC and others to develop and spread these stewardship programs. We do need to promote the development and use of rapid diagnostics to empower physicians to more accurately prescribe antibiotics, and finally, we need to pass the STAR Act, which will give us federal oversight and create the infrastructure necessary to gather the data we need to understand the scope of the antibiotic resistance problem in this country.

We also need a multi-pronged approach to promoting antibiotic restoration. We need to establish orphan drug-like economic push and pull incentives to rekindle interest in the industry in antibiotic R&D. We need to increase funding to relevant federal agencies like NIH, like BARDA and we should really start thinking seriously about establishing a nonprofit public-private partnership whose mission is to develop critically needed small-market molecules to treat life-threatening infections caused by resistant bacteria, and finally, we need to continue to promote regulatory clarity at the FDA for existing pathways and also to create new pathways to create critically needed antibiotics that have not been developed previously.

I am going to close with a brief anecdote. Congressman Burgess mentioned penicillin. I want to go back to the beginning of the penicillin era to remind all of us how important it is that we have effective antibiotics. So I am going to tell you the true story of a 4-year-old girl in late 1942 who had been in perfect health until she suddenly developed an infection on her face, a skin infection. This progressed relentlessly. Her face and neck became so swollen, she could not swallow her own saliva, and it was when she began gasping for breath that her parents in a panic rushed her to the Mayo Clinic.

[Slide.]

And this is what this little girl looked like on arrival to the hospital. Her parents were told that she would be dead within 2 days and there wasn't anything anybody could do to stop it. Imagine being told that about your 4-year-old that 4 days earlier had been in perfect health. But she was lucky because Dr. Horel at the Mayo Clinic was one of the very few people in the United States that had access to penicillin before the end of World War II. He went into

his laboratory. He grabbed some doses of penicillin and he began treating her, and this is what this little girl looked like at the end of a few days of penicillin therapy.

Antibiotics are the only medical intervention that can take a patient that looks as sick as this little girl did on arrival to the hospital and turn them into somebody as well as she looked when she was discharged from the hospital a few days later. To my understanding from what I am told, this little girl is alive and well today and still receives her care at the Mayo Clinic. Penicillin has given her a 7-decade lease on life and counting.

[Slide.]

So this is my final slide. Prior generations have given us the gift of antibiotics and today we have a moral obligation to ensure that antibiotics continue to be available for our children and future generations. The time for debate has passed. The time for action is now. Thank you.

[The prepared statement of Dr. Spellberg follows:]



**Testimony of the Infectious Diseases Society
of America (IDSA)**

**Antibiotic Resistance: Promoting Critically
Needed Antibiotic Research and
Development and Appropriate Use
("Stewardship") of these Precious Drugs**

Presented by Brad Spellberg, MD, FIDSA

**Before the House Committee on Energy and
Commerce Subcommittee on Health**

June 9, 2010

The Infectious Diseases Society of America's (IDSA) Statement on
Antibiotic Resistance: Promoting Critically Needed Antibiotic Research and
Development and the Appropriate Use ("Stewardship") of these Precious Drugs
Before the House Committee on Energy and Commerce Subcommittee on Health
June 9, 2010

The Infectious Diseases Society of America (IDSA) appreciates this opportunity to speak in support of the House Energy and Commerce Committee Health Subcommittee's efforts to promote the development of new antibacterial drugs ("antibiotics") for humans, as well as methods to ensure the judicious use of such antibiotics once they are on the market. [1] My name is Brad Spellberg, MD, FIDSA. I am an infectious diseases specialist and an Associate Professor of Medicine at the Geffen School of Medicine at the University of California, Los Angeles (UCLA). I also work within the Division of General Internal Medicine at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. I am a member of IDSA's Antimicrobial Availability Task Force and the author of a book titled "Rising Plague: The Global Threat from Deadly Bacteria and Our Diminishing Arsenal to Fight Them."

IDSA represents more than 9,000 infectious diseases physicians and scientists devoted to patient care, prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis (TB) and HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negative bacterial infections such as *Acinetobacter baumannii* (which are attacking brave U.S. soldiers who have served in Iraq and Afghanistan) and *Pseudomonas aeruginosa*, and, finally, emerging infections like the 2009 H1N1 influenza virus.

ANTIBIOTIC RESISTANCE: A MAJOR PUBLIC HEALTH PROBLEM

Antibiotic resistance is a serious public health, patient care and safety, and national security issue. Antibiotic-resistant infections are extremely difficult to treat and frequently recur. These infections result in tremendous pain, suffering, and disfigurement in adults, children and infants, and have caused millions of deaths worldwide. Hospital-acquired antibiotic-resistant infections currently kill nearly one hundred thousand Americans each year (this does not include infections acquired outside of hospitals) and have been estimated to cost the U.S. health care system between \$21 billion and \$34 billion annually.

"The last decade has seen the inexorable proliferation of a host of antibiotic-resistant bacteria, or bad bugs, not just MRSA, but other insidious players as well. ... For these bacteria, the pipeline of new antibiotics is verging on empty. 'What do you do when you're faced with an infection, with a very sick patient, and you get a lab report back and every single drug is listed as resistant?' asked Dr.

Fred Tenover of the Centers for Disease Control and Prevention (CDC). 'This is a major blooming public health crisis.'"

—*Science* magazine; July 18, 2008 ^[2]

For the past decade, IDSA has raised concerns about the imbalance between the dwindling antibiotic pipeline and the significant and concomitant need for new antibiotics to treat an increasing number of drug-resistant infections. In 2004, concluding that immediate government action was essential, IDSA published its report "Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates a Public Health Crisis Brews," ^[3] and launched an advocacy campaign to spur government solutions. Now, six years later, the drug pipeline and resistance problems have only grown worse as more companies have withdrawn from antibiotic research and development (R&D) and ever-more resistant "bad bugs" have spread across the United States in health care settings and communities, devastating the lives of the young and the old, the healthy and the frail.

In response to the expanding crisis, IDSA recently launched the *10 x '20 initiative* ^[4], endorsed by other prominent medical societies and organizations ^[5], to provide a measurable goal and a framework for global action. The inaugural statement appears in the April 15th issue of the journal *Clinical Infectious Diseases*. The *10 x '20* goals are simple to articulate, but difficult to achieve. We seek a global commitment by the United States Government, particularly the Department of Health and Human Services (HHS), and other governments to create a sustainable antibiotic R&D enterprise, which in the short-term can produce 10 new safe and effective antibiotics by 2020. The antibiotics we seek are those that can treat the most serious and life-threatening pathogens against which most approved antibiotics are not effective. ^[6,7]

Today, IDSA's statement before the Subcommittee explores our fundamental premise that:

- Antibiotics are a vital resource and a precious gift from prior generations, and we have a moral obligation to ensure this resource is available for future generations.
- Safe and effective antibiotics are urgently needed to treat serious and life-threatening infections caused by a growing list of drug-resistant bacteria.
- As with other diminishing resources (energy, forests, etc.), Congress and the Administration must establish policy (statutory and administrative) ^[8,9] to nurture both the conservation and restoration of antibiotics through the development of new, innovative antibiotics and other relevant tools (rapid diagnostics, vaccines, etc.).
- We must adopt, promote, and continue to refine effective strategies to prevent the emergence and transmission of resistant organisms. Antibiotics must be used judiciously in order to limit the emergence of drug-resistant bacteria. Antibiotic stewardship strategies are the best way to achieve this goal, while good infection control practices and immunization policies can prevent transmission of these organisms.

ANTIBIOTICS' TRUE VALUE: "PRECIOUS RESOURCE" OR "A GIVEAWAY MARKETING TOOL"?

Our society takes antibiotics for granted—we do not realize how fortunate we are to have them. Many of our parents, grandparents and great-parents were not so lucky. Prior to the discovery of antibiotics, many injuries and illnesses became death sentences as there was no way to treat the common infections that were often associated with them. Since antibiotics were first discovered and used in the 1930s and then in the 1940s to save American soldiers during World War II, they have saved millions of lives and eased the suffering of an incalculable number of patients. Indeed, antibiotics often are referred to as "miracle drugs," as patients need only take them for a few days to completely resolve most infections.

"For most of the infectious diseases on the wards of Boston City Hospital in 1937, there was nothing that could be done beyond bed rest and good nursing care. Then came the explosive news of sulfanilamide [the first antibiotic], and the start of the real revolution in medicine. ... I remember the astonishment when the first cases of [lethal blood infections] were treated with antibiotics in Boston in 1937. The phenomenon was almost beyond belief. Here were moribund patients, who would surely have died without treatment, improving...within a matter of hours...and feeling entirely well within the next day...we became convinced, overnight, that nothing lay beyond reach for the future. Medicine was off and running."

—Lewis Thomas, MD, "Notes of a Medicine Watcher," 1983

How have we spiraled from such a high starting point, where antibiotics were recognized as an "awesome acquisition of power" and "a force for change in the 20th century of the same general kind as James Watt's modification of the steam engine," (according to Walsh McDermott, MD, first president of the Medical Board [precursor to the Institute of Medicine] of the National Academy of Sciences) to the low point today where grocery stores and pharmacies give prescribed antibiotics away for free as a marketing ploy to lure customers into their stores? As a society, we need to begin to rethink how we utilize these precious resources.

There is incredible disparity in how our society values antibiotics versus other types of medicines. Most commonly used antibiotics cost only a few dollars for the typical course of treatment. It is arguable that effective antibiotics provide greater value than any other medicine ever created. The most expensive antibiotics (e.g., linezolid and daptomycin) can cost between \$1,000 and \$3,000 for a seven-day course of treatment (compared to \$20,000-\$50,000 for a multi-week course of a typical cancer treatment). The investment made in purchasing antibiotics typically leads to a total cure of the target disease or infection and a life saved. One antibiotic course has the potential to provide a sick child 70 or more quality years of life. That was not the case prior to the 1940s, when there was a much higher probability that a child with a serious infection would not survive. Antibiotic therapy also reduces the risk that communicable bacteria will spread to other susceptible patients. Hence, a single course of antibiotics has the potential to

protect and preserve many quality years of life for many people. No other type of medicine can claim such an achievement at such a price.

With this value in mind, as a society we are justified in seeking new and innovative ways to protect the long-term effectiveness and availability of antibiotics.

We must begin to think “outside the box” about this problem. The moral imperative to have effective antibiotics available, combined with the failure of all efforts attempted to date to slow resistance and stimulate R&D, indicates that we need to think more broadly and more creatively about the problem and its solutions.

ANTIBIOTICS ARE UNIQUE

In addition to their extremely high level of effectiveness and the value that they provide to society, antibiotics are unique among all medicines in two critically important ways. First, over time, antibiotics lose their ability to treat the diseases for which they were approved—due to bacteria’s ability to mutate and develop resistance to the antibiotic. Second, due to resistance and our desire to prolong antibiotics’ effectiveness for as long as possible, physicians and professional societies ask that antibiotics be used appropriately and sparingly and seek ways to limit misuse and abuse of these drugs. We actively discourage non-essential use of newly approved antibiotics.

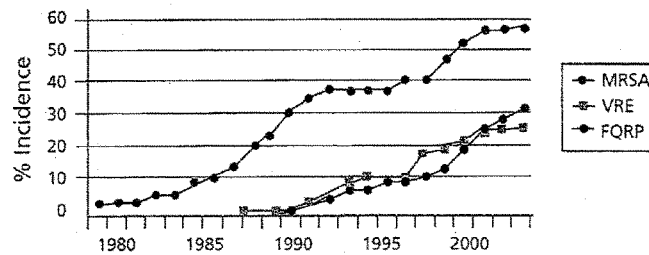
Unfortunately, this combination of factors—antibiotics’ ability to cure most infections in just a matter of a few days, antibiotic resistance, and measures to ensure appropriate use (“antibiotic stewardship”) to protect antibiotics’ effectiveness over time—has resulted in a market failure. Most pharmaceutical companies have withdrawn from antibiotic R&D to pursue more lucrative markets such as treatments for chronic diseases (e.g., heart disease, high blood pressure, anti-cholesterol, etc). The sad result is that the antibiotic pipeline now is drying up, placing Americans and other people around the world at serious risk. ^[10,11]

In a report ^[12] published in the January 2009 issue of the journal *Clinical Infectious Diseases (CID)*, IDSA confirmed that the antibiotic pipeline is nearly bare, particularly for drugs needed to treat high priority pathogens and infections. In September 2009, the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) released their own report ^[13] affirming IDSA’s assessment and found only 15 antibiotics in development that may provide benefit over existing drugs. Based on experience, we know most of these drugs will never make it across the finish line to approval. Furthermore, none of the drugs currently in development is capable of treating bacteria that are resistant to all presently available drugs.

The bottom line: The relentless spread of a growing number of drug-resistant infections in our hospitals and communities (for example, see Chart 1) and the diminishing number of antibiotics being approved (see Table 1) have made it more and more difficult for physicians to protect patients and save lives—morbidity and mortality are on the rise. The dearth of new antibiotics in development is deeply troubling to health experts and has the

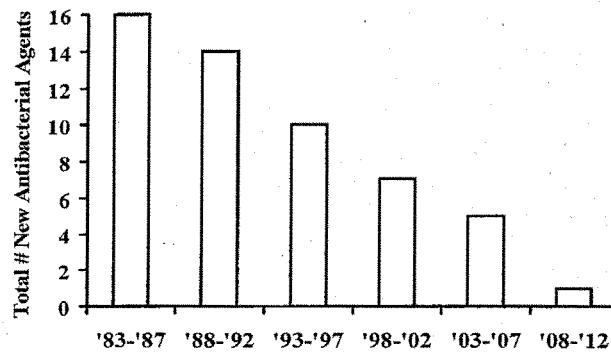
potential to change the practice of medicine as we know it. A number of advanced interventions that we currently take for granted—e.g. surgery, cancer treatment, transplantation and care of premature babies—would be impossible to perform without effective antibiotics.

Chart 1: Resistant Strains Spread Rapidly



Source: Centers for Disease Control and Prevention

Table 1: Antibiotic Approvals (1983-Present)



Source: IDSA's 2004 Bad Bugs, No Drugs report (modified)

ANTIBIOTIC RESISTANCE: THE COSTS ARE TOO GREAT TO WAIT

The U.S. CDC has described antibiotic resistance as “one of the world’s most pressing health problems” as “the number of bacteria resistant to antibiotics has increased in the last decade [and] ... many bacterial infections are becoming resistant to the most commonly prescribed antibiotic treatments.” The World Health Organization (WHO) has identified antibiotic resistance as “one of the three greatest threats to human health.”

Infectious diseases physicians agree. The costs due to antibiotic resistance, both in the numbers of lives lost or devastated as well as in economic terms, are exceedingly high.

Deaths and Illnesses

The compelling and heart-wrenching stories witnessed by infectious diseases specialists and other physicians on a daily basis are represented briefly in the patient stories and recent statistics that follow. As you will see, there is urgent need to act.

Patient Stories:



Simon was a healthy baby boy from **Chicago, Illinois** who contracted MRSA and did not survive his infection.

— “At the emergency room, I tried to convince myself that this was all much ado about nothing. Well, I was wrong. Way wrong. As soon as Simon was wheeled in, doctors hooked him up to everything imaginable (oxygen, nebulizer, IVs for medication and pain relievers). And, I kept hearing, “Your child is very, very sick. Your child is very, very sick.” At this point, I became absolutely hysterical... Simon kept looking at me with his chocolate-brown eyes, and long, curly eye-lashes, repeating, ‘Agua, agua ... agua.’ Now I have a window into what so many families experienced 50 years ago—the death of a child caused by a bacterium or virus. It is ironic that the same advances in science that led to healthier and longer lives have resulted in the unintended consequence of the creation of bacteria that no longer respond to antibiotics. As long as we do not treat antibiotics as a precious resource, only to be used in the most extreme cases, we will continue to have a false sense of security in medicine.”

— Everly Macario, DrPH, Simon’s mother



Rebecca Lohsen was a healthy 17-year old high school honor student and swimmer from **Northern New Jersey** who died of an MRSA infection in 2006.

— “I no longer have the confidence in medicine that I once had...I’ve watched the dismay in the faces of doctors who are supposed to be the

best in their field as they told me they didn't have any more "cures in their bag."

—Linda Lohsen, Rebecca's mother, a former public health nurse



Carlos Don was a healthy 12-year old football player and skateboarder from **Southern California** who died of pneumonia caused by an MRSA infection.

—"I lost my son Carlos to MRSA on February 4, 2007, only 15 days before his 13th birthday. Carlos was the person I loved most in this entire world. He was my life."

—Amber Don, Carlos' mother



Ricky Lannetti was a healthy 21-year old football player at Lycoming College in **Williamsport, Pennsylvania** who contracted MRSA and did not survive the infection.

—"Like millions of Americans today, I had never heard of MRSA until it claimed my son's life. His sisters, father and I live everyday thinking about Ricky and what he would be doing today if he was here... During a time that I should have been planning for my son's college graduation and helping him prepare for his future, I was burying my only son who only days before had been the picture of health."

—Theresa Drew, Ricky Lannetti's mother



Tom Dukes was a healthy and active father from **Lomita California** whose life was torn apart by a painful and drug-resistant *Escherichia coli* (*E. coli*) in December 2009.

*—"You're going to the operating room right now" the emergency room doctor told me. My family gathered around me...I said goodbye, scared I wouldn't see them again. Months later, I'm still trying to get my life back together after an antibiotic-resistant *E. coli* infection turned my world upside down."*

—Tom Dukes, *E. coli* survivor

Recent Statistics:

- A CDC-supported study ^[14,15] published in the *Journal of the American Medical Association (JAMA)*, October 17, 2007) estimated that invasive MRSA infects more than 94,000 people and kills nearly 19,000 people annually around the country—more deaths than those caused by emphysema, HIV/AIDS, Parkinson's

disease and homicide. These numbers are very conservative, since they only consider infections proven by laboratory culture—many more cases occur for which physicians do not request cultures. Moreover, invasive MRSA infections represent only a segment of the greater MRSA problem in this country.^[16]

- CDC reports^[17] that nearly 2 million health care-associated infections (HAIs) and 90,000 HAI-related deaths occur annually in the U.S. Many of these infections and deaths are caused by antibiotic-resistant infections.
- A February 2010^[18] study published in the *Archives of Internal Medicine* showed that two common conditions caused by HAIs—sepsis and pneumonia—killed 48,000 people and ramped up health care costs by \$8.1 billion in 2006 alone.
- A December 2009 *JAMA* study^[19] showed that 1 in every 2 patients in more than 1,000 ICUs in 75 countries were infected—infected patients had twice the risk of death in the hospital than uninfected patients.

In IDSA's estimation, the above patient stories and recent statistics represent only the tip of the iceberg. The United States needs better surveillance and data collection tools (see the STAAR Act discussion below) to adequately understand the full extent of the impact of antibiotic-resistant infections.

Health Care Costs Associated with Antibiotic-Resistant Infections

The direct and indirect economic costs associated with antibiotic-resistant infections are enormous in terms of dollars spent, length of hospital stays, and loss of productivity.

- A recent analysis of antibiotic-resistant infection data conducted at Chicago Cook County Hospital^[20] showed that the direct and indirect economic costs of antibiotic resistance are substantial in terms of dollars and length of hospital stays. Extrapolating the analysis nationwide^[21], the authors concluded that antibiotic-resistant infections cost the U.S. health care system in excess of \$20 billion annually as well as more than \$35 billion in societal costs, and more than 8 million additional days spent in the hospital.
- Another recent study^[22] published in 2009 in *Antimicrobial Agents and Chemotherapy* comparing HAIs caused by drug-resistant gram negative bacteria versus drug-susceptible gram negative bacteria, found that the drug-resistant infections increased hospital costs by 29.3 percent (\$144K vs. \$106K) and lengths of stay by 23.8 percent (36 vs. 31 days).
- A 2010 study in *Infection Control and Hospital Epidemiology*^[23] found that over a six-month period of assessment the cost of treating patients with MRSA was significantly higher than treating patients with *S. aureus* that responds to methicillin, known as methicillin-susceptible *S. aureus* (MSSA). The median cost for treating an MRSA infection was \$34,657 compared to \$15,923 for treatment

of an MSSA infection. The higher costs were the result of longer hospital stays, more laboratory and imaging tests, and more rehabilitation services.

PRIORITY ANTIBIOTIC-RESISTANT BACTERIA PATHOGENS

Listed below are some of the current drug-resistant infections of greatest concern.

The ESKAPE Pathogens: The so-called ESKAPE ^[24] Pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *ESBL positive bacteria*, such as *E. coli* and *Enterobacter* species) represent a grouping of antibiotic-resistant gram-positive and gram-negative bacteria ^[25] that cause the majority of U.S. HAIs. The group is so-named because these bacteria effectively “escape” the effects of most approved antibacterial drugs.

Take for example, *Acinetobacter baumannii*, an increasingly common drug-resistant bacteria found in health care settings across the United States ^[26,27] and globally. *Acinetobacter* is multidrug-resistant, and is extremely difficult to kill once it enters the body. ^[28] In just the past 10 years in the U.S., the frequency of *Acinetobacter* resistant to all first-line antibiotics has risen from less than 5 percent (of isolates studied) to greater than 40 percent. As a result, *Acinetobacter* now often is treatable only with a highly toxic drug, colistin, which was abandoned in the 1960s because it causes kidney damage. Increasingly *Acinetobacter* has become resistant even to colistin, and hence those infections are totally untreatable with any available antibiotic. Of note, *Acinetobacter* has become a particular problem for U.S. soldiers who have served in Iraq and Afghanistan. A 2006 study ^[29] conducted at Walter Reed Army Medical Center found that of 75 patients who tested positive for the bacteria, 89 percent were resistant to at least three classes of antibiotics and 15 percent were resistant to five classes. The bacteria also are able to live on environmental surfaces in hospitals placing additional soldiers and patients at risk. *Acinetobacter* is commonly found in water and soil in Iraq, Afghanistan and other locations, and the bacteria can enter the body through deep combat wounds or burns. Once inside the bloodstream, the bacteria can wreak havoc causing potentially fatal infections, including pneumonia, meningitis, and shock. A strong soldier may survive a combat injury sustained in Iraq or Afghanistan, only to lose the battle against *Acinetobacter*.

Like MRSA ^[16], vancomycin-resistant *Staphylococcus aureus* (VRSA) ^[30], is a strain of *Staph* bacteria that is multi-drug resistant. Although extremely rare at this time, VRSA is especially problematic as it is resistant to vancomycin, the powerful antibiotic physicians often use when others fail. Should this dangerous organism begin to spread further, we will be in dire straits. A patient with a VRSA infection was transferred from a hospital in Delaware to a hospital in Pennsylvania in April 2010. This is the 11th known case of VRSA in the United States. Eight prior cases occurred in Michigan. The others occurred in New York and Delaware.

Clostridium difficile: Another resistant infection receiving increased scrutiny is *Clostridium difficile* (*C. diff*). ^[31,32,33] *C. diff*. is an HAI that can lead to severe diarrhea,

rupture of the colon, kidney failure, blood poisoning, and death. CDC estimates there are 500,000 cases of *C. diff.* infection annually in the U.S., contributing to between 15,000 and 30,000 deaths. States have reported increased rates of *C. diff.* nationwide over the past several years noting more severe disease and an associated increase in mortality. Elderly hospitalized patients are at especially high risk.

COMPREHENSIVE U.S. GOVERNMENT ACTION IS URGENTLY NEEDED

"The impacts of antibiotic-resistant bacteria can be reduced by preserving the effectiveness of current antibiotics through infection control, vaccination and prudent use of antibiotics, and by developing new antibiotics specifically to treat infections caused by antibiotic-resistant bacteria."

—Congressional Office of Technology Assessment (OTA), September 1995 ^[34]

Similar to the OTA, IDSA supports a comprehensive, multi-pronged approach to address the complex problem of antibiotic resistance. We believe success can be achieved if we:

- A. fix the broken antibiotic drug pipeline;
- B. support the development and utilization of new rapid diagnostic tests;
- C. enact the Strategies to Address Antimicrobial Resistance (STAAR) Act (H.R. 2400);
- D. promote the judicious use of antibiotics in human medicine (antimicrobial stewardship);
- E. implement effective infection prevention and control programs;
- F. support the development of new vaccines and appropriate immunization policies;
- G. stop non-judicious uses of antibiotics on U.S. farms (animal and plant agriculture); and
- H. view antibiotic resistance as a global health issue.

For the purpose of today's hearing, IDSA will focus primarily on the first four elements.

A. Fix the Broken Antibiotic Pipeline

In IDSA's view, there is an urgent need to address the factors that have resulted in a dearth of new antibiotics in development: lack of financial incentives of sufficient strength to make companies choose to engage; regulatory uncertainty caused by the lack of consistent approval pathways at the Food and Drug Administration (FDA); insufficient federally supported research; the need for greater public/private collaborations; and lack of adequate rapid, point-of-care diagnostics (see diagnostics discussion in section B below).

Strengthen Financial Incentives

To fix the broken pipeline and create a sustainable, national and global antibiotic R&D enterprise, it is necessary to determine the right combination of financial incentives ("push" and "pull" mechanisms) to entice industry to reengage in antibiotic R&D. ^[35,36,37] Examples of the push incentives are grants, contracts, and tax credits. Examples of the

pull incentives are guaranteed markets, liability protection, patent extensions or data exclusivity, and prizes. These incentives are intended to change the “return on investment” or net present value calculation of antibiotics to make them more competitive with other drugs. Such incentives were discussed in detail in IDSA’s 2004 “Bad Bugs, No Drugs” white paper.^[3] More recently, a September 2009 report commissioned by the European Union and produced by Chantal Morel and Elias Mossialos of the London School of Economics and Political Science (LSEPS) provides a comprehensive list of incentives that should be helpful to members of the Subcommittee as they deliberate these issues. The LSEPS incentives are summarized in brief in a newly published (May 2010) *British Journal of Medicine* analysis^[38] also authored by Morel and Mossialos.

IDSA supports in particular an extension of patent life for priority antibiotics effective against emerging multidrug resistant bacteria. These drugs are viewed as priority drugs as opposed to low priority drugs (“me-too” drugs) that add little to the existing inventory. IDSA supports the development of an antibacterial orphan-like pathway for drugs shown as safe and effective in the treatment of infections due to the drug-resistant high priority bacteria. This orphan drug-like designation could extend by several years (perhaps up to 15 or 20 years) the period of market exclusivity during which no generic drugs could be approved. The additional years of patent life/market exclusivity could motivate companies to develop drugs against priority pathogens and infections. Obviously, other push/pull incentives listed in the LSEPS paper (tax credits, grants, awards, advanced market commitments, etc.) also should be considered. We emphasize that the failure of antibiotic R&D has occurred along the entire spectrum of drug discovery and development—there is no single rate-limiting step to overcome. Therefore, adopting a single type of incentive will not solve the problem. Rather, a panel of push and pull incentives, which can appeal to the various constituents (e.g., large and small companies, academia, etc.) active along the entire R&D spectrum, must be created.

Advance Regulatory Certainty

FDA must quickly assure a clear regulatory pathway for the development of antibiotics. For many years, industry representatives have identified regulatory uncertainty as one of the primary obstacles to new antibiotic development. IDSA acknowledges the strong commitment expressed by current FDA leaders and staff to address the multi-faceted problem of regulatory uncertainty. Despite good faith meetings, workshops, and advisory committee meetings, the situation today appears no better than it was at this time last year. In some respects, the level of uncertainty has increased.^[39,40]

For example, in March 2009, a draft guidance providing an approval pathway for new drugs for community-acquired bacterial pneumonia (CABP) was published and public comment solicited. We were extremely pleased to finally have witnessed some progress. However, the public comments lead to an additional advisory committee meeting last December, which again has engendered uncertainty. We, and the pharmaceutical industry, still are waiting for publication of the final guidance for trials in CABP patients. Similarly, in May 2009, companies were moving forward on clinical trials for new drugs to treat skin and skin structure infections (SSSIs), but, in 2010, companies no longer

know what to do to satisfy FDA on SSSIs even though such a pathway had existed for years. Clear clinical trial design guidance is urgently needed for CABP and complicated SSSIs, as well as for other serious infections such as hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, and bacteremia.

Also, in 2010, FDA has moved no closer to identifying an approval pathway that will lead to new antibiotics to treat multiply drug-resistant and pan-drug-resistant pathogens like *Pseudomonas aeruginosa*, *Acinetobacter*, Extended Spectrum Beta Lactamase (ESBL) – producing *E. coli* and *Klebsiella*, and *Klebsiella pneumoniae carbapenemase* (KPC) producing gram-negative bacteria. According to the CDC, KPC producing bacteria are quickly spreading across the United States. For these life-threatening, multiply drug-resistant bacteria, which occur in critically ill patients that are difficult to enroll in clinical trials, IDSA believes it is time to discuss a new model for the assessment of potentially active new drugs; a model that allows for FDA approval based on a relatively small clinical sample size (< 100 patients) with infections in multiple organ systems. Perhaps Congress also should consider some type of conditional approval mechanism for these drugs.

To quickly implement changes in the regulatory process requires people and money. This spring, IDSA testified ^[41] in support of an additional \$36 million for FDA's antibiotic resistance and antibiotic drug review programs. Specifically, we support an additional \$15 million to allow the agency to hire additional staff to develop much needed clinical trial guidance documents and to fund Critical Path initiatives specific to antibiotic drug development. We also requested \$13.25 million to support a focus on new antibiotics within FDA's new regulatory science initiative with the National Institutes of Health (NIH). The regulatory science initiative involves the development and use of new tools, standards and approaches to more efficiently develop products and to more effectively evaluate product safety, efficacy and quality.

Finally, industry representatives also have articulated a strong desire for greater harmonization of international regulatory review and approval standards for antibiotics across the U.S., Europe, Japan, etc. as competing standards serve as impediments to approval.

Strengthen Funding for Resistance and Drug and Diagnostics Discovery Research

Significantly increased federal research dollars are urgently needed to advance scientific knowledge about resistance to antibiotics as well as to support drug discovery and development. Given the scope of the antibiotic resistance problem and its potential impact on every American, IDSA supports ^[42] a substantial funding increase in antibacterial resistance and antibacterial discovery research within NIH's National Institute of Allergy and Infectious Diseases (NIAID) to a total of \$500 million in FY2011. We also support a significant boost in funding for HHS' Biomedical Advanced Research and Development Authority (BARDA), including specific funding targeting antibiotic development. IDSA recommends that at least \$1.7 billion of multi-year appropriations be allocated to BARDA in FY 2011 to fund therapeutics, diagnostics, vaccines, and other technologies, including antibiotics. IDSA also wishes to see BARDA take a much stronger role in advancing the

development of new antibiotics to treat the ESKAPE pathogens and *C. diff.*, which are affecting a significant number of Americans in hospitals annually. Regardless of whether these particular drug-resistant bacteria present an immediate bioterrorism threat, that potential is always there.

After IDSA performed a preliminary examination of NIAID research funding for Fiscal Year 2009, NIAID officials graciously provided pertinent grant data and undertook a more in-depth review. Of a total NIAID grant budget of roughly \$4.7 billion, \$242 million funded grants in the areas of antibiotic resistance and discovery or development of new antibacterials. IDSA's analysis of this additional information finds that many of these grants funded pathogenesis, descriptive epidemiology, and other facets of the problem, as opposed to research on resistance mechanisms or new approaches to antibacterial therapy. Further, funding specifically for drug or other treatment modalities was \$114 million, of which \$94 million was for drugs or other therapies for agents of bioterrorism (e.g., anthrax, plague, botulism). Only \$16 million was provided for grants that focus on efforts to detect and develop new drugs for infections due to the ESKAPE pathogens.

Because of the rapid escalation in the problem of resistance, new initiatives must be developed. Significantly increasing funding both related to antibacterial resistance research and antibacterial drug discovery will enable NIAID to support a better understanding of mechanisms of resistance as well as expanding joint ventures between academia and industry that will identify new drug targets and drugs with activity for those targets. In the end, we hope this will lead to the development of a library of target drug compounds that will support industry's efforts to find new antibiotics that treat infections caused by ESKAPE pathogens and *C. diff.*, etc. Increased funding for NIAID and BARDA also will help federal officials work with industry and academia to create a seamless approach to new antibiotic drug R&D.

New funding also is needed to support the development of new vaccines and rapid diagnostics (see diagnostics discussion in Section B below). It is well-known that the development and use of pneumococcal conjugate vaccine has led to a reduction in drug-resistant *Streptococcus pneumoniae* as well as a reduction in antibiotic use.^[43] Development of new vaccines for MRSA and other multi-drug resistant organisms would be very useful in preventing diseases caused by these organisms as well as in reducing antibiotic use.

Establish Public Private Collaborations

For multiply drug-resistant bacteria and other high priority bacterial infections, where market challenges are extreme, we should explore the establishment of a non-profit, public-private partnership (PPP). Since a PPP would not be profit-driven, it could focus on developing critically needed drugs for indications where markets are very small (e.g. drugs to treat *Acinetobacter*, *Klebsiella*). Removing profit motives from the equation also will help to limit the marketing of the "priority" antibiotic to the more serious and life-threatening indication for which it is approved. This will support the appropriate stewardship of these drugs and will prolong their effectiveness. Thus, the advantage of

the PPP is that it could merge antibiotic conservation efforts with new antibiotic R&D efforts.

It is important to note that the PPP idea is not meant to replace the essential activities of private companies in drug discovery and development. Rather the PPP is intended to complement efforts to reinvigorate market driven, for-profit antibiotic development. Private companies' R&D activities must still be strengthened through strong, new incentives and other companies must be lured back into this field. We cannot rely on an unproven PPP model to fix the current situation.

Create an Antibiotic Innovation and Conservation Fee

One idea we propose for funding new antibiotic innovations and the uptake of good antimicrobial stewardship practices is the creation of an Antibiotic Innovation and Conservation (AIC) fee. Such a fee would be placed on every course of antibiotic treatment prescribed both on human and veterinary prescriptions (branded and generic). Perhaps 75 percent of the AIC fee could be allocated to the development of promising, high priority candidate antibiotics under a PPP arrangement while 25 percent of the fee could go to a fund overseen by the CDC, which would support the promotion and establishment of antibiotic stewardship programs in health care facilities across the country. In addition to funding new R&D, an advantage to such a fee is that it could help to limit non-judicious uses of these drugs in both human and animal settings. Finally, the AIC fee would recognize the value of these essential drugs and the need to use them wisely.

B. Support the Development and Utilization of New Rapid Diagnostic Tests

Rapid, point-of-care diagnostic tests are an important part of the solution and are urgently needed for three reasons:

1. The biggest driver of inappropriate antibiotic use is the inability of physicians to be certain whether or not patients have a bacterial infection, and if so, what type of bacteria is causing the infection. Using existing test methods (culture tests) requires days or weeks to identify bacterial organisms, and the tests often fail to detect bacteria that are present (i.e. the culture tests are not "sensitive"). The power of a rapid, accurate diagnostic that could inform the physician that the disease is not, in fact, a bacterial infection cannot be overestimated. Such a test would dramatically reduce inappropriate antibiotic prescriptions. Furthermore, if the patient did have a bacterial infection and the test could identify which bacteria was causing the infection, it would enable more accurate, narrow spectrum antibiotics to be prescribed, further improving antibiotic stewardship efforts.
2. New rapid diagnostic tests would greatly facilitate clinical trials of critically needed new antibiotics. The tests would enable investigators to identify potential study subjects more easily, which would permit smaller and less expensive studies of antibiotics as they move through development. Smaller and less expensive studies would facilitate development of new antibiotic agents.

3. New diagnostics would make it easier to identify and track the spread of new and dangerous drug-resistant pathogens (e.g., KPC-producing bacteria) as they spread across the country. Once we are better able to track the spread of these organisms, we can begin to study and implement interventions to slow their pace.

Unfortunately, while some other areas of medicine have made tremendous strides in advancing technological sophistication, there has been little impetus for diagnostics companies to develop new tests to detect and identify resistant bacteria. This is partly due to the fact that physicians have come to treat infections empirically, often not utilizing microbiologic diagnostic tests to confirm their diagnoses. With the low cost of currently available generic antibiotics, it actually costs more to test patients than to just give them a prescription. As we have seen above, the failure to establish a precise cause of infection results in guesswork in antibiotic use, overprescribing, and less than optimal patient care.

For these reasons, we believe it is necessary to enact incentives that spur the development and utilization of rapid diagnostics tests. The LSEPS report can be helpful in this regard, but we also need to consider how the Center for Medicare and Medicaid Services (CMS) and Joint Commission can support the uptake and use of these essential tools.

To support the development of new diagnostics, we ask Congress to establish and fund a reference library of culture-positive clinical specimens, perhaps maintained by NIH or FDA's Center for Devices and Radiological Health. Such a reference library would allow sponsors of new diagnostics to quickly determine the sensitivity and specificity of their new test to detect pertinent pathogens (viruses and bacteria) in clinically relevant specimens. The library would consist of clinical specimens that are fully characterized as to the presence, or absence, of relevant microorganisms as determined by current standards of laboratory diagnosis.

C. Enact the Strategies to Address Antimicrobial Resistance (STAAR) Act

IDSA and 25 other organizations ^[44,45] representing physicians, hospitals, pharmacists, health care epidemiologists, infection prevention and control professionals, and public health experts and advocates have strongly endorsed the Strategies to Address Antimicrobial Resistance (STAAR) Act, H.R. 2400, and launched the STAAR Act Coalition to support the bill's enactment.

The STAAR Act ^[46,47,48,49,50] builds upon the solutions identified in the OTA report as well as on existing federal efforts that have been highlighted in the Public Health Action Plan to Combat Antimicrobial Resistance. The Action Plan was published in January 2001 by an interagency task force, co-chaired by CDC, FDA and NIAID, and authorized under Section 319E ^[51] of the Public Health Service Act. This authorization expired September 30, 2006. Thirteen key elements (out of a total of 84 elements) highlighted within the Action Plan were deemed critically necessary to address the growing resistance crisis. Unfortunately, neither the interagency task force nor the Action Plan

has received adequate resources to accomplish its goals. Moreover, there exists no centralized office to facilitate the coordination of activities, prioritize the federal response, or provide a platform for on-going discussion and action. Nor is there a sufficient process for engaging outside experts to provide input into federal policymaking in this area.

The STAAR Act strengthens existing efforts by establishing an Antimicrobial Resistance Office (ARO) within the HHS Office of the Assistant Secretary of Health. The Director of ARO will serve as the director of the existing interagency task force. The Act also establishes a Public Health Antimicrobial Advisory Board (PHAAB) comprised of infectious diseases and public health experts who will provide much-needed advice to the ARO Director and task force about antimicrobial resistance and strategies to address it. The STAAR Act will strengthen existing surveillance, data collection, and research activities as a means to reduce the inappropriate use of antimicrobials, develop and test new interventions to limit the spread of resistant organisms, and create new tools to detect, prevent and treat drug-resistant “bad bugs.”

Public reporting of infections and access to data provides the opportunity for states and the CDC to rapidly identify problems and work toward corrections and improvements that save lives. Such data on antibiotic-resistant infections and antibiotic use are needed to inform our development of antibiotic stewardship programs, to limit the emergence and prevent transmission of resistant bacteria, and to guide development of new and effective therapies. The U.S. desperately needs transparent and accurate data with respect to antibiotic resistance and antibiotic use.

The lack of comprehensive data on use and resistance is a problem that is unique to the United States, among developed nations. In contrast, the European Union has a robust data collection system that has been able to track antimicrobial use and resistance trends, by country, since 1999. Data also are available by specific antimicrobial drug and specific pathogen. Having comparable data is critically important if the U.S. is to tackle the antibiotic resistance problem. We strongly support including within the STAAR Act language to ensure that we have the data needed to make the best decisions possible regarding antibiotic use, both in human health and agricultural settings.

D. Promote the Judicious Use of Antibiotics in Human Medicine

Inappropriate use of antibiotics is one of the biggest contributors to the problem of resistance. It has been estimated that up to 50 percent of antibiotic use is either unnecessary or inappropriate, and this holds true across all health care settings, including acute care academic and community hospitals, long-term care facilities, private physician offices, and at the retail pharmacy and consumer level. (Inappropriate use also is an enormous problem in food animal/agricultural settings, but we have not been asked to focus on this significant issue.^[52,53]) As mentioned earlier, in the past several years there have been a variety of campaigns by retail pharmacies that offer “free” antibiotics. The intent is to attract customers, but it further contributes to a public perception that

antibiotics can be used for any type of illness and that there are no health-related repercussions associated with their use.

Promoting Antibiotic Stewardship Strategies in Health Care Facilities

The primary strategy for preserving antibiotics and preventing the development of drug resistance is antibiotic stewardship, which is intended to ensure that antibiotics are used appropriately.^[54] Antibiotic stewardship has been a major focus for both IDSA and the Society for Healthcare Epidemiology of America (SHEA); both societies are collaborating to promote good stewardship practices in health care, but practical implementation has been challenging.

The goal of antibiotic stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the emergence of resistance, and the selection of pathogenic organisms such as *C. diff*. The combination of effective antibiotic stewardship along with comprehensive infection prevention and control efforts has been shown to limit the emergence and transmission of antibiotic-resistant bacteria. A secondary goal of antibiotic stewardship is to reduce health care costs without adversely affecting quality of care. Indeed, many studies have demonstrated that antibiotic stewardship can decrease health care costs while improving the quality of care. Antibiotic stewardship strategies directly improve cure rates by ensuring that patients receive the correct antibiotic in a timely fashion. Improved cure rates result in decreased intensive care unit and overall length of stay. Antibiotic stewardship programs are typically directed by a physician and/or a clinical pharmacist with relevant (infectious diseases, etc.) training.

IDSA and SHEA issued guidelines for developing an institutional program to enhance antibiotic stewardship in 2007.^[55] These guidelines provide an extensive blueprint for designing and implementing a successful stewardship program. However, establishing an antibiotic stewardship program can be a costly endeavor that eludes many health care facilities that lack adequate resources. While stewardship programs have demonstrated a long-term cost savings, they require staff resources that some health care facilities may not have. Specifically, not every health care facility has an infectious diseases physician or an infectious diseases pharmacist on staff that can help to develop, monitor, and oversee a stewardship program. Other facilities may have staff with appropriate training, but the facility may be unable—or unwilling—to compensate the physician or pharmacist for the extra time required to establish and maintain these programs. Regardless of the costs of establishing and maintaining a stewardship program, in this age of resistance, it is too costly not to practice stewardship.

It is possible for health care facilities to implement stewardship strategies and embrace a philosophy of stewardship without having to implement an expensive comprehensive program. While most research has focused on comprehensive efforts, they may not be practical in smaller community hospitals and practice settings. In these instances, there are a fair number of administrative and practice strategies that can be employed to pick the “low hanging fruit.”

Essential Components of Successful Antibiotic Stewardship Programs

There are several essential components of a successful stewardship program: leadership and dedicated staff; training and education; mechanisms that serve to improve antibiotic usage; diagnostic utilization (see Section B above for a discussion on diagnostics); and a mechanism to pay for establishing and maintaining these programs and practices and the staff's services.

Leadership and Dedicated Staff

To assure the success of stewardship programs, the hospital administrator must be an active proponent to ensure that the programs have the necessary infrastructure, the ability to track and manage use data and that the staff working on stewardship are compensated for their time. Also critical is the support of medical staff leadership—or physician champions—to develop and maintain stewardship programs, while also encouraging staff buy-in and adherence to the stewardship philosophy.

Training and Education

Training and educating health care professionals on the appropriate use of antibiotics must include appropriate selection, dosing, route, and duration of antibiotic therapy. To ensure that training and education is working, there should be extensive collaboration between the antibiotic stewardship and hospital infection prevention and control teams. Without benchmarks, it is difficult to track successes and weaknesses.

Education must occur at all levels, including the executive and administrative levels. The training and education component also should include a mechanism for quality control audits and feedback.

Improving Use

Another critical component of successful stewardship efforts is conserving our limited antibiotic resources. Once health care facility staff is trained and educated about antibiotic stewardship strategies, including appropriate use, dose and duration, there are additional strategies to further improve the use of certain antibiotics. This can take the form of restricting which antibiotics are included in the formulary or requiring that prescribing a specific therapy may require a preauthorization. Additional mechanisms can include antibiotic order forms, formal prospective audit and feedback, de-escalation of therapy based upon microbiology data, an evaluation of dose optimization, or the conversion from intravenous to oral therapy.

Antibiotic usage also can be improved by changing prescribing requirements, so that prescriptions include the type of antibiotic, the quantity, dose, duration and indication. Including all of these items on a prescription could allow for their capture by electronic health records, which in turn, allows for public reporting and monitoring by the health care facility or by an outside entity. The special labeling also can be restricted to certain antibiotics that are directed toward our most resistant pathogens, have a greater potential to cause resistance, or have increased potential for toxicity.

Paying for Antibiotic Stewardship

Given the importance of antibiotics to public health, patient care and safety, and national security, we need to think of novel ways to promote the uptake of good antibiotic stewardship practices. Government-supported enticements would go a long way to promote the adoption of stewardship programs and practices by health care facilities, to help to ensure quality across these programs nationwide, and to promote leadership in this field. The Antibiotic Innovation and Conservation fee we mentioned above is one potential funding option. Adoption of antibiotic stewardship strategies also could be a component of value-based purchasing.

CDC Programs Related to Antibiotic Stewardship, Use and Resistance

To combat inappropriate use of antibiotics, the CDC launched the program, Get Smart: Know When Antibiotics Work, to educate the public and providers about the judicious use of antibiotics. Physicians sometimes admit that they inappropriately prescribe antibiotics to patients who insist on receiving them. As part of CDC's effort to help health care professionals, the Get Smart program includes tools to educate patients as well as tools to assist physicians in explaining to their patients why antibiotics would be unnecessary in a particular treatment protocol. Information is disseminated in a manner accessible to the greater public, such as podcasts and health e-cards, but there is still a need for a more aggressive campaign targeted at consumers.

Building on the success of the existing "Get Smart" program, the CDC recently launched a new antibiotic stewardship initiative—"Get Smart for Healthcare"—in hopes of advancing adherence to stewardship practices in health care facilities. CDC officials are collaborating with physicians and hospitals about the best ways to implement the campaign, which aims to clearly define the roles of physicians, pharmacists and other health care workers in antibiotic stewardship initiatives. The CDC is working with SHEA to develop simple implementation tools to facilitate adoption of these efforts.

The CDC also is collaborating with the Institute for Healthcare Improvement (IHI) and SHEA to develop a driver diagram with practical antibiotic stewardship implementation strategies with the intent of promoting aspects of care in places where improvement is needed. A long-term goal of this partnership is to encourage more facilities to engage in appropriate antibiotic use and stewardship efforts.

In an effort to more adequately capture antibiotic use data the CDC will pilot an Antimicrobial Use and Resistance (AUR) Module in the fall of 2010 as part of the National Healthcare Safety Network (NHSN) system. The module likely will include a pharmacy option, which measures antibiotic use by days of therapy, and a microbiology option, which will assist health care facilities by providing data that allows for benchmarking.

Finally, related to CDC's funding, we call to your attention the Administration's proposed budget for FY 2011, in which CDC's already severely strapped Antimicrobial Resistance budget would be cut dramatically by \$8.6 million—just over 50 percent! This vital program is necessary to help combat the rising crisis of antibiotic resistance. Yet the

President's FY2011 budget would allow only 20 state and local health departments and health care systems to be funded for surveillance, prevention, and control of antibiotic resistance, down from 48 this past year. It would also eliminate all grants to states for the Get Smart in the Community program to combat improper uses of antibiotics. IDSA believes CDC's antimicrobial resistance activities are so important to protecting Americans from serious and life-threatening infections that we should boost funding for these activities to at least \$40 million in FY2011.

CONCLUSION

As we have outlined above, the problems of antibiotic resistance and the dry antibiotic pipeline are complex and multi-factorial. No one single strategy can begin to address these problems—a multi-pronged approach is required. We must conserve antibiotics' effectiveness through the adoption of appropriate antibiotic stewardship practices. We must prevent the emergence and transmission of resistant infections through effective infection prevention and control initiatives and effective immunization policies. And we must continue to replenish this precious resource through heightened investments in innovative antibiotics and related rapid diagnostics, and through the adoption of strong, well-considered incentives.

Last November, President Barack Obama and Swedish Prime Minister Fredrik Reinfeldt, representing the European Union (EU), agreed to establish a Transatlantic Task Force to address antibiotic resistance. The Task Force will focus on appropriate therapeutic use of antibiotics in the medical and veterinary communities, prevention of both health care- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antibiotics. IDSA strongly supports ^[56] this comprehensive approach, but it must move forward with a sense of extreme urgency to strengthen the antibiotic and related diagnostics pipelines.

The Subcommittee on Health has a long history of leading the way to address our nation's most pressing public health issues. Today, we call on you to adopt strong measures to build and sustain a global antibiotic (and related rapid diagnostics) R&D enterprise. It is our hope that the resulting enterprise will spur the development of 10 new safe and effective antibiotics by 2020. Such an achievement would be of immense benefit to the health of the citizens of the United States and the world. Further, a sustained infrastructure would help to reestablish the highly skilled scientific workforce that has been lost over the past two decades as many companies abandoned antibiotic development. We also urge the Committee to move with haste to enact the Strategies to Address Antimicrobial Resistance Act, which we believe will significantly strengthen U.S. antibiotic resistance surveillance, research, prevention and control efforts as well as provide the necessary data we need to save lives and protect public health.

Thank you again for the opportunity to testify on this incredibly important issue. IDSA looks forward to assisting the Subcommittee in any way that we can.

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Mr. PALLONE. Thank you, Dr. Spellberg.
Dr. Fryhofer.

STATEMENT OF SANDRA FRYHOFER

Dr. FRYHOFER. Good morning, or is it afternoon now? Chairman Pallone, Ranking Member Shimkus and other members of the subcommittee, I am Dr. Sandra Adamson Fryhofer. I am a general internist in Atlanta, Georgia. I am a clinical associate professor of medicine at Emory University School of Medicine. I am a member of the American Medical Association's Council on Science and Public Health, and I am pleased to testify today on behalf of the AMA about antibiotics and the growing threat of antibiotic resistance.

Antibiotics are miracle drugs but many are beginning to lose their luster. Antibiotic resistance is now a major public health concern. Take MRSA, for example, methicillin-resistant *Staph aureus*. You can think of MRSA as a rogue staph infection. The bacteria is smarter, so traditional antibiotics in the methicillin family can't kill it. MRSA infections aren't new. The new trend is where we are seeing them. They used to be seen only in hospital settings but now we are seeing these infections in the community and in otherwise healthy young people including athletes. The AMA believes that in order to reverse these trends requires a multi-faceted approach: reduce inappropriate use of existing antibiotics, incentive research and development in order to create new antibiotics, and finally, encourage alternatives to reduce our dependence on antibiotics, and one such alternative is vaccines.

Inappropriate use of antibiotics, why is this important? Increasing rates of drug-resistant invasive infections correlate directly with increases in antibiotics overuse. Decreasing inappropriate use of antibiotics can reduce the prevalence of antibiotic-resistant bacterial infections or super bugs. Continued physician education about this issue is key. The AMA has sponsored many educational conferences. We have developed and disseminated educational tools including one specifically focusing on MRSA. We have issued scientific reports on antibiotic resistance. We have also supported the CDC's campaign to prevent antimicrobial resistance in health care settings.

The Physician Consortia for Performance Improvement called PCPI was convened by the AMA. Now, this group is dedicated to improving patient health, safety and quality of care. PCPI develops evidence-based clinical performance measures and they have already developed one for managing ear infections in children and they are in the early stages of developing one for managing sinus infections in adults.

Next, patient education must also be a part of the solution. One of the main reasons that physicians prescribe unnecessary antibiotics is patients want them and some of them demand them. The AMA helped launch the CDC's Get Smart public education campaign on why physicians should not prescribe antibiotics for the common cold. The AMA has been involved in several media briefings about antibiotic resistance, and hopefully as mainstream media gives more attention to this issue, our patients may become more accepting of why they don't need an antibiotic.

Now, we have talked a lot today about use of antibiotics in the health care system but use of antibiotics in agriculture and in animal husbandry also contributes to antibiotic resistance. The AMA is opposed to use of antibiotics at non-therapeutic levels in agriculture or as growth promoters and urges that such use be terminated or phased out based on sound scientific risk assessments.

Another part of the solution is we need new antibiotics, especially now that many of the ones we have no longer work. This means fostering and incentivizing new research and development. The AMA has supposed the call to action you just heard about, the “Bad Bugs, No Drugs” and another new initiative that Dr. Spellberg told us about, the 10 by 20, is very exciting. This initiative will be considered for endorsement by the American Medical Association at our annual meeting later this week.

So patient education, physician education, new antibiotics. We also need to look for innovative ways to reduce our dependence on antibiotics. One way of staving off infection is through vaccines, and the development of new vaccines against resistant bugs like toxigenic *E. coli*, for example, should be encouraged. However, vaccines only work if people get them. We have vaccines available that boost immunity to deadly strains of pneumococcal infection, but even in this era of ever-increasing antibiotic resistance, immunization rates against pneumococcal infection remain low in adults.

In summary, the American Medical Association is committed to getting antibiotic resistance under control and we are making some headway. CDC data over the last 10 years shows a 20 percent decrease in use of antibiotics to treat upper respiratory infections and a 13 percent decrease in prescribing antibiotics overall for all office visits. The American Medical Association will continue to support these efforts and we appreciate the opportunity to be here with you today.

[The prepared statement of Dr. Fryhofer follows:]



Statement

of the

American Medical Association

to the

**Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives**

**Re: Promoting the Development of Antibiotics and
Ensuring Judicious Use in Humans**

Presented by:

**Sandra Adamson Fryhofer, MD, MACP, FRCP
Member, AMA Council on Science and Public Health**

June 9, 2010

**Statement
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June 9, 2010

Good morning Chairman Waxman, Chairman Pallone, Ranking Member Shimkus, and members of the Subcommittee. My name is Sandra Adamson Fryhofer, MD, MACP, FRCP, and I am a member of the Council on Science and Public Health (CSAPH) of the American Medical Association (AMA). I am a general internist engaged in private practice in Atlanta, Georgia, and a Clinical Associate Professor of Medicine at Emory University School of Medicine. I am pleased to be able to testify today on behalf of the AMA. The AMA commends the Subcommittee for its continued focus on the important issue of promoting the judicious use of antibiotics in humans.

Overview

Antibiotic resistance has been a major public health concern for many years. The problem has continued to increase in prevalence with bacteria. Resistance is a complicated phenomenon that involves the environment and the patient, as well as the microbe. Thus, resistance may arise as a result of therapy or as a result of a previous exposure to a given drug or its analog, or may be intrinsic to the microbe itself. Additionally, resistance is found not only in the hospital environment but also in the community setting and in long-term care facilities, with some hospital outbreaks directly traceable to resistant bacteria introduced from the community.

The AMA believes that the problem of increasing antibiotic resistance is an important public health concern. In order to preserve the utility of these important drugs for the future, it is critical that we manage this problem collaboratively and consider all possible areas for intervention. The AMA believes that a multi-faceted approach is needed comprised of: (1) reducing the inappropriate use of existing antibiotics to preserve their clinical utility; (2) incentivizing the research and development pipeline in order to create novel antibiotics for clinical use; and (3) developing and implementing alternative interventions to reduce dependence on antibiotics. The following testimony focuses to a large degree on the first of these approaches, namely the inappropriate or overuse of antibiotics by physicians.

Reducing inappropriate use

AMA efforts in reducing inappropriate use have focused on three issues: (1) educating primary care physicians on the importance of reducing the inappropriate use of antibiotics in their patients; (2) informing patients about the public health impact of increasing antibiotic resistance; and (3) reducing the inappropriate use of antibiotics in animal agriculture.

AMA policy urges physicians to educate patients about their antimicrobial therapy, the importance of compliance with the prescribed regimen, and the problem of antimicrobial resistance. It also urges that physicians and physicians-in-training are educated continuously about the appropriate prescribing of antimicrobial agents and encourages the use of multidisciplinary and cooperative antibiotic resistance management programs (*H-100.973 Combating Antimicrobial Resistance through Education*). The AMA and physician organizations comprising the AMA's Federation of Medicine are acutely aware of the profession's role in reducing inappropriate antibiotic use and for many years have taken aggressive steps to support judicious use of antibiotics in clinical practice. For example, the use of critical last-resort and new antibiotics, (e.g., vancomycin, streptogramins, linezolid) is monitored, restricted, and controlled by hospital infection control committees. Likewise, procedures to limit or contain the spread of resistant organisms have been actively developed and implemented. In 2005, the AMA supported the Centers for Disease Control and Prevention's (CDC) Campaign to Prevent Antimicrobial Resistance in Healthcare Settings and disseminated information on the campaign to its medical specialty society members and provided links for downloading materials from the CDC website.

Existing data indicate that control strategies implemented in hospitals have reduced the incidence of resistant bacteria. Additionally, optimal selection, dose, and duration of treatment are helping to prevent the development of antibiotic resistance in bacteria. Adjusting hospital antibiotic formulary practices reduces the incidence of specific resistant bacteria, but ongoing surveillance is necessary to guard against the emergence of other resistant bacterial strains. Improved surveillance provides critical information on the emergence and epidemiology of new resistant strains, and the genotypic basis of such resistance, as well as data on appropriate therapeutic options. Studies are now showing that such efforts along with education-based methods are changing the prescribing habits

of physicians. Significantly, cooperation between infection-control specialists, infectious disease specialists, clinical pharmacists, and the microbiology laboratory provides useful real time information pertaining to antibiotic choice and dosing for prescribing physicians.

Antibiotic resistance in the community remains problematic. It continues to manifest, for example, through the appearance of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), which has received significant media attention in recent years. Additionally, the use of antibiotics for the treatment of pediatric acute otitis media has not subsided despite the issuance of a “watchful waiting” guidance from the American Academy of Family Physicians (AAFP) and the American Academy of Pediatrics (AAP) almost six years ago. Thus, continued outreach on specific situations where inappropriate antibiotic use still occurs is required.

The AMA has used (and continues to use) various communication tools to increase education and outreach to primary care physicians in private practice on the topic of antibiotic resistance. For example, the AMA has sponsored educational conferences, developed and disseminated educational tools (e.g., a special patient page in the *Journal of the American Medical Association*) and treatment algorithms (including a recent tool on CA-MRSA), and issued scientific reports on specific aspects of antibiotic resistance. The AMA has also supported and publicized primary care practice recommendations with respect to appropriate use of antibiotics. These include a series of “Principles for Appropriate Antibiotic Use” developed by the American College of Physicians in 2001 for adult patients, and several pediatric guidelines that were published more than a decade ago. In particular, the AMA collaborated with the California Medical Association Foundation to move its state-specific Alliance Working for Antibiotic Resistance Education (AWARE) practice guidelines compendia to a national level. The AWARE compendia summarizes and incorporates practice guidelines from multiple authorities on appropriate antibiotic use for several conditions into two easy-to-read documents: one covering pediatric guidelines and the other covering adult guidelines.

The AMA-convened Physician Consortium for Performance Improvement (PCPI) is a national physician-led initiative dedicated to improving patient health and safety. More than 170 members comprise the PCPI, including national medical specialty societies, state medical societies, the American Board of Medical Specialties, health care professional organizations, federal agencies, individual members and other groups interested in improving the quality of care. The PCPI identifies and develops evidence-based clinical performance measures and measurement resources that enhance quality of patient care and foster accountability and promotes the implementation of relevant clinical performance improvement activities. Recognizing the importance of improving the quality of care with respect to judicious antibiotic prescribing, the PCPI has begun to look at developing performance measures that consider this issue.

For example, a performance measure set was developed in consultation with the American Academy of Pediatrics, American Academy of Otolaryngology Head and Neck Surgery Foundation, and the Centers for Medicare and Medicaid Services for the

management of pediatric patients with acute otitis externa and acute otitis media with effusion. The measure set focused in part on avoidance of inappropriate use of systemic antimicrobial therapy. Pediatric patients 2 years and older with diffuse uncomplicated acute otitis externa should generally be managed with topical preparations. Similarly, acute otitis media with effusion in pediatric patients 2 months through 12 years of age usually resolves spontaneously. Systemic antibiotics do not have long-term efficacy and are not recommended for routine management. The measure is derived from the percentage of patients with these diagnoses who were not prescribed systemic antimicrobial therapy unless documentation of medical reason(s) for prescribing systemic antimicrobial therapy was evident. A measure set on adult sinusitis is in the early stages of development for 2010.

Recognizing that the abuse of antibiotics is commonplace in the developing world, the AMA worked with the World Medical Association (WMA) to develop the WMA's 2008 Declaration and Policy Statement on antibiotic resistance. This statement provided targeted policy guidance to: (1) federal governments; (2) national medical associations; and, (3) practicing physicians.

Finally, a primary reason that physicians prescribe unnecessary antibiotics to patients is the patient's desire to receive the antibiotic. Accordingly, the AMA has engaged in several efforts to educate patients and the public on the importance of appropriate antibiotic use. The AMA also has sponsored media briefings on infectious disease topics with a focus on antibiotic resistance, and along with the American Academy of Family Physicians, the AMA participated in the launch of the CDC's "Get Smart" campaign. This campaign targeted the public to educate them on the negative impact of antibiotic resistance on public health as well as individual health and wellness and explained why physicians should not prescribe antibiotics for the common cold. The ultimate goal of the "Get Smart" campaign was to promote appropriate antibiotic use in the community. At the launch of "Get Smart" in 2003, the AMA acknowledged the importance of the campaign and the AMA's unique position to not only increase knowledge and awareness of appropriate antibiotic use among the public and physicians, but also to stimulate appropriate dialogue between patients and their physicians.

It is clear that inappropriate antibiotic use in medical settings, coupled with liberal prescribing practices, previously contributed to the increase in antibiotic resistance. It is also now clear that attention to this issue has improved clinical decision-making on the appropriate use of antibiotics in human medicine. However, we must remain aware that whenever antibiotics are used, the threat for selection of antibiotic-resistant bacteria persists. Such strains of bacteria may enter the human health care system and be amplified and perpetuated. Accordingly, all avenues by which resistant strains can enter the human health care system remain relevant, including the use of antibiotics in food animals. AMA policy states our opposition to the use of antibiotics at non-therapeutic levels in agriculture, or as pesticides or growth promoters, and urges that non-therapeutic use in animals of antibiotics (that are also used in humans) should be terminated or phased out based on scientifically sound risk assessments (*H-440.895 Antimicrobial Use and Resistance*).

The AMA believes that pilot programs examining the impact of eliminating the use of antibiotics in animal husbandry are appropriate. Such an approach would provide data on how farmers can best adapt to changes in agricultural techniques, and would identify best practices for the gradual elimination of the use of antibiotics in agriculture. In order to affect the change necessary to eliminate inappropriate use in animal husbandry, the AMA participated in the FDA's process to develop their draft Guidance for Industry, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Antimicrobial Effects on Bacteria of Human Health Concern." The AMA has also supported different legislative initiatives to curtail such use, including H.R. 2400, the Strategies to Address Antimicrobial Resistance Act, and H.R. 1549/S. 619, the Preservation of Antibiotics for Medical Treatment Act.

Incentivizing new research and development

The improvement in managing antibiotic resistance within the medical community stems in large part from significant changes in physician prescribing behavior and the aggressive implementation of judicious use and critical "last resort" policies within medical facilities. However, these policies may create a disincentive for research and development of novel antibiotics. Pharmaceutical companies are reluctant to invest in developing a new antibiotic only to be confronted with stringent use paradigms dictated by clinical management strategies, as necessary as they are. Thus, innovative incentives must be developed to foster continued research and development of novel antibiotics to ensure that these important tools to combat infectious diseases remain available for future generations of physicians. The urgency of this situation has been highlighted by a major effort from the Infectious Diseases Society of America. Their first initiative was the call-to-action titled "Bad Bugs, No Drugs," released in 2004 and supported by the AMA. This white paper is now being followed by the "10 by '20" initiative. The goal of this initiative, launched in May of 2010, is to create incentives for manufacturers to develop 10 new antibiotics by 2020. The AMA will be considering endorsement of the "10 by '20" initiative at its June 2010 Annual Meeting.

Reducing dependence on antibiotics

As antibiotic resistance continues to be a problem and the antibiotic pipeline remains stagnant, we should also examine innovative ways to reduce our dependence on antibiotics. As mentioned above, rigorous infection control strategies implemented in hospitals have been successful in limiting the spread of resistant organisms. The development of new vaccines against pathogens with clinically important levels of resistance should be encouraged (e.g. *E. coli*) even as we promote the use of existing vaccines. Of particular note, in the era of increasing antibiotic resistance in *Streptococcus pneumoniae* (pneumococcus) strains, it is disappointing that immunization rates against pneumococcus remain low in adults.

Conclusion

While significant improvements have occurred with respect to judicious use of antibiotics in medical facilities and in physician prescribing behavior, antibiotic resistance remains a major public health problem. Continued vigilance and education to maintain appropriate prescribing practices in physicians, proper use behaviors in patients, and improved surveillance for emergence of resistance are all necessary. The continued use of antibiotics that have a human health impact in animal husbandry remains a major public health problem. Also of particular concern is stagnation in the development of novel antibiotic agents; new processes are necessary to incentivize the research and development of new, clinically important antibiotics.

The AMA recognizes that antibiotic resistance must be controlled through judicious use of antibiotics by health care professionals and will continue to encourage the federal government, the World Health Organization, the World Medical Association, and the International Federation of Pharmacists to promote more effective education on the appropriate use of antibiotics. The AMA will continue to support physicians in their efforts to educate their patients about antibiotic therapy, the importance of compliance with the prescribed regimen, and the problem of antibiotic resistance. The AMA will also continue to educate physicians and physicians-in-training about the appropriate prescribing of antibiotics while encouraging the implementation of multidisciplinary and cooperative antibiotic resistance management programs that include participation of infectious disease physicians, infection-control specialists, microbiology laboratory personnel, and clinical pharmacists.

Mr. PALLONE. Thank you, Doctor.
Dr. Bradley.

STATEMENT OF JOHN S. BRADLEY

Dr. BRADLEY. Thank you very much, Mr. Chairman. It is a real pleasure to be here today to share some information with you about children. My name is John Bradley. I am a fellow of the American Academy of Pediatrics, or the AAP, which is a nonprofit professional organization of more than 60,000 primary care pediatricians, pediatric medical subspecialists and pediatric surgical specialists dedicated to the health, safety and well-being of infants, children and adolescents. I am a member of the Academy's committee on infectious disease, and with Dr. Spellberg, the IDSA's task force on antimicrobial drug availability. My oral testimony this morning is going to focus specifically on the challenges of antibiotic resistance in children.

The successful treatment of infections in children requires the availability of safe and effective antimicrobial therapy and especially for children I emphasize both safe and effective. Antimicrobials are among the most commonly prescribed drugs in children but the appropriate use of antibiotics in the treatment of true infections, and kids do get otitis media and strep throat, combined with the inappropriate use of antibiotics has led to the development of resistance. This resistance has had a significant impact on our ability to treat children in both clinics and in hospitals. Antibiotic choices for treatment of infections are more limited for children than adults. However, we have the same critical need for new antibiotics in children as is present in adults as these same antibiotic-resistant organisms that cause infections in adults cause infections in children who are hospitalized. However, for most of the newer, more potent antibiotics approved for adults over the past 5 to 10 years, inadequate information exists on the safety and efficacy of these antibiotics in newborns, infants and children but we are using them anyway because we have to.

Please consider the following specific pediatric issues. First, children are uniquely vulnerable to infections. Newborn infants, particularly premature infants who are now surviving with birth weights of only 1 pound, babies this large, have horribly suppressed immunity that is a necessary component of survival during growth in the womb. In addition, all children up to age 2 years have immature immune systems and are particularly susceptible to bacterial bloodstream infections and spinal meningitis. Further, many infants have anatomic or genetic abnormalities that increase their susceptibility to infection and many of these children die of infections during childhood, so my colleagues who care for adults have never taken care of these children or watched them die.

Second, the safety of drugs is a critical factor for children, a population that the FDA and human research committees recognize as vulnerable. Drug toxicity such as irritation or damage to the brain, heart, bones or joints may last a lifetime.

Third, damage from the infection itself may last a lifetime, particularly if the wrong antibiotic is used for the treatment of an antibiotic-resistant organism.

Fourth, children are incredibly efficient at spreading infections. Not only do they cough, sneeze and drool over each other, but they spread infection to siblings, parents and grandparents. Diarrhea is a scourge of daycare centers. Clean diaper-changing facilities and sinks are critical but are often lacking, and the CDC and public health departments around the country have documented many outbreaks of bacterial infections in infants caused by increasingly resistant bacteria as we reported in our written testimony. Antibiotic resistance is a serious problem in children, and the AAP has worked for over a decade to teach pediatricians and families about judicious use of antibiotics beginning in earnest in 1998 with our collaboration with the CDC in a series of articles published in our official medical journal called *Pediatrics*. We have shared CDC materials. We have created AAP materials to distribute to our members and to the families they care for and to emphasize over and over again the importance of appropriate use. One toddler in a daycare center who receives inappropriate therapy leading to the development of resistant bacteria can spread that organism to classmates and family members, making treatment of both the child and the contacts including adults more difficult. We know this and we are committed to programs to enhance appropriate use to decrease resistance.

Just like our colleagues in adult medicine, we are running out of antibiotics for these multi-resistant bacteria, and in our written testimony we provide a current reference to a journal article describing the deaths of four out of seven premature infants who were exposed to an antibiotic-resistant strain of *acinetobacter*, the gram-negative bacteria that is coming back from Iran and Iraq in our soldiers.

Vaccination is another critical component of combating the spread and severity of antimicrobial-resistant infections, and the AAP has taken pride in being the professional pediatric organization that has developed and promoted an immunization schedule for all children in the United States for the past 72 years. Universal immunization of children for pneumococcus, the antibiotic-resistant bacteria that infects the respiratory tract, causes ear infections and pneumonia, has actually decreased antibiotic resistance in invasive infections in both children and adults as immunization prevents this resistant bacteria from living in the nose and throat of immunized children, therefore limiting the spread of these bacteria to adults who kiss them and share food with them.

In summary, antibiotic resistance is a moving target and requires ongoing intense commitments to develop better surveillance tools, better vaccines and better antibiotics. We support the initiatives that were presented by Dr. Spellberg from the IDSA and notably H.R. 2400, or the STAR Act. The Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act have helped us tremendously encouraging the pharmaceutical industry to develop information on pediatrics that they ordinarily would not have done.

I have just a few slides that I would like to show of premature infants here just to give you an idea of how small and frail they are, and some of the slides that I wish to show——

Mr. PALLONE. Dr. Bradley, I know you are like a minute and a half over so——

Dr. BRADLEY. I am sorry.

Mr. PALLONE. Just show us the slides and then we will move on.

Dr. BRADLEY. Yes, sir.

[Slide.]

This is a gut infection in a newborn infant resistant. This is MRSA destroying the lung, and Dr. Spellberg showed the picture of this child who is posted on the IDSA Web site. This is a child who had open heart surgery for congenital heart disease and is now on a lung bypass machine, and he is such a setup for antibiotic-resistant bacteria.

Thank you. I appreciate the opportunity to testify.

[The prepared statement of Dr. Bradley follows:]



**TESTIMONY OF JOHN S. BRADLEY, MD FAAP
ON BEHALF OF THE AMERICAN ACADEMY OF PEDIATRICS**

**“Antibiotic Resistance and the Impact on the Health of Children: the Need for More Safe
and Effective Antibiotics and Better Antimicrobial Stewardship”**

**COMMITTEE ON ENERGY AND COMMERCE HEALTH SUBCOMMITTEE
U.S. HOUSE OF REPRESENTATIVES**

June 9, 2010

AAP Department of Federal Affairs
The Homer Building
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Good morning. I appreciate the opportunity to testify today before the House Energy and Water Subcommittee on Health regarding antimicrobial resistance. My name is John Bradley, MD, FAAP, and I am proud to represent the American Academy of Pediatrics (AAP), a non-profit professional organization of more than 60,000 primary care pediatricians, pediatric medical sub-specialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults.

I currently am the Chief of the Division of Infectious Diseases, Department of Pediatrics at the University of California, School of Medicine and the Clinical Director of the Division of Infectious Diseases at the Rady Children's Hospital San Diego. I am a member of American Academy of Pediatrics' Committee on Infectious Diseases and the Infectious Diseases Society of America's (IDSA's) Task Force on Antimicrobial Drug Availability.

As prior witnesses have spent a great deal of time and attention on defining the increasing problem of antibiotic resistance among humans – including statistics on numbers of adult and pediatric patients infected by resistant bacteria and the financial impact on the US healthcare system outlined by the IDSA just moments ago – my comments will focus more specifically on the challenges it presents to the health of pediatric populations.

Children Are Not Little Adults

Infectious diseases have a significant impact upon American children. Children contract infections more often than adults and are more likely to spread infections to playmates, schoolmates, siblings, parents and grandparents.

Our recent national experience with the 2009 H1N1 influenza, as well documented by the Centers for Disease Control and Prevention (CDC), provides a striking picture of just how vulnerable children are to infection, and how quickly infections can be spread in communities by infants and school-aged children. Both viral infections and bacterial infections, including those caused by antibiotic-resistant bacteria, have been documented to

spread easily among children and from children to adults. Antibiotic-resistant bacterial pathogens have the potential to cause widespread injury and suffering, and even death, in children.

Perhaps one of the most pressing reasons to find better ways to address the uncontrolled spread of antibiotic resistance is that damage to the child lasts a lifetime. A school-aged child with a devastating bone infection that involves the growth plate will never have normal growth of his or her leg, will need multiple corrective surgeries, and will never quite regain normal function. Worse, the death of a child from antibiotic-resistant bacteria in 2010 is an unpardonable tragedy. With all our resources and expertise in prevention, as well as drug discovery and development, it is unconscionable not to have an effective therapy for each and every bacterial infection.

Concerns Specific to Infants and Children

Antibiotic-resistant bacteria are increasingly prevalent in hospitals as well as in the community. Newborn infants are a particularly vulnerable target for bacterial infections, as their immune systems are immature and suppressed to assure growth in the womb. In the United States, approximately 12% of infants are born prematurely. Premature infants are being successfully cared for at lower and lower birth weights, with many infants born now who weigh only a single pound having a good chance for survival. However, these premature infants' skin and major organ systems are not fully developed, leading to an even greater susceptibility to infections of the skin, lung and intestines. And because many of these very premature infants must remain in the Neonatal Intensive Care Unit for weeks and they require a number of life saving procedures, they are at risk for infection with bacteria which survive in the NICU because they are resistant to antibiotics.

In addition, many infants are born with anatomic defects that require aggressive and extensive corrective surgeries very early in life in order to survive. These infants may spend many weeks in the hospital as they adapt to life with their newly constructed

anatomy. Infants with congenital heart disease represent one such group that are at high risk of post-operative wound infections after major open-chest and open-heart reconstructive surgery.

Young children with certain genetically inherited diseases may not survive to adulthood due to chronic and recurrent infections caused by antibiotic-resistant bacteria. The most well-known of these pediatric disorders are cystic fibrosis and chronic granulomatous disease. These children are extremely susceptible to recurrent infections requiring many courses of antibiotics, and ultimately are infected by multi-drug resistant bacteria, mycobacteria, and fungi that are exceedingly challenging to treat.

Certain infections are unique to children due to developmental and growth characteristics. One such infection is called acute hematogenous osteomyelitis, or bone infection. This infection is characteristic of young adolescents whose bones are growing at their fastest rates, who are very active and continually sustain minor injury to their bones and joints during normal daily physical activity and sports.

Staph bacteria are the most common cause of infections, and over the past 10 years many major pediatric centers in the United States have now documented a dramatic rise in bone infections caused by a new, antibiotic-resistant strain of staph, called MRSA (methicillin-resistant *Staphylococcus aureus*). While reports from every pediatric hospital in the United States document the increased destruction of bone and muscle tissue caused by MRSA, the most dramatic and life-threatening complications occur when MRSA spreads to the bloodstream.

The most detailed published reports concerning MRSA infections have come from Texas Children's Hospital in Houston. In one case, a child with a bone infection in his leg who was not responding to antibiotic treatment actually required a filter to be surgically implanted in his veins to trap the bacteria as they entered his bloodstream from his infected legs. This extreme measure was necessary to prevent MRSA from spreading to his lungs,

where the bacteria were creating an increasing number of large abscesses and progressive pneumonia, putting the child's life in danger.

Many of the bacteria that cause infections in adults also cause infections in neonates, infants and children, including not only the previously mentioned MRSA bacteria, but also the ESKAPE bacteria (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and ESBL positive *E. coli*).¹

Several recent reports now document an increasing and very disturbing trend regarding the significant impact that antibiotic resistance bacteria are having on the health of children. A report published this year from the National Children's Medical Center in Washington, DC, documented that MRSA bacteria infections in the neonatal intensive care unit were responsible for increasing the length of hospital stay by a mean of 40 days, and were associated with an average extra charge of \$164,301 per baby.²

Last year, a report from a neonatal intensive care unit in Long Island, New York, provided information about the spread of a highly antibiotic-resistant *Acinetobacter baumannii*.³ This bacterium was recovered from 7 neonates, 4 of whom died. All affected neonates were born between at 23 to 26 weeks of gestation (approximately 6 months) and weighed between 430 and 720 grams (1 to 2 pounds) at the time of exposure to *Acinetobacter*, which was resistant to all commonly used antibiotics for the newborn. While the bacteria were susceptible to only one FDA-approved antibiotic for newborn infants, this antibiotic has never been studied systematically in such premature infants, forcing pediatricians to use an antibiotic for which no safety or efficacy data are available.

Another study⁴ published in a manuscript last year investigated the rise of antibiotic resistant (ESBL) *E. coli* and *Klebsiella* (two of the ESKAPE bacteria) in children in the Salt Lake City region, and documented a three-fold increase between 2003 and 2007.

Another article from the Pediatric Intensive Care Unit at Johns Hopkins University Medical Center in Baltimore published in December of 2008⁵ documented the entry into their unit of vancomycin-resistant enterococcus (VRE), a resistant organism that has primarily been associated with infections in adults. When these investigators began systematically looking for this resistant organism in babies, they found a rate that was 5 times higher than they previously suspected.

While *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* primarily cause infections in hospitalized patients, certain other bacteria tend to cause more disease in otherwise healthy children living in communities. Antibiotic-resistant community pathogens with particular impact for children include MRSA and *Streptococcus pneumoniae* (the most common cause of ear infections, sinus infections, and pneumonia and often referred to as “pneumococcus”). Even with appropriate use of antibiotics to treat bona fide infections in children, pneumococcal bacteria will develop resistance.

Stopping the spread of drug resistant infections among infants and children presents a unique challenge. Good personal hygiene, especially thorough hand-washing, usually keeps infections from spreading between adults who have runny noses, coughs, sneezes, and even diarrhea; however, these good health habits are not part of normal behavior for toddlers and young school-aged children.

National strategies to combat the rapid spread of H1N1 influenza actually included the closing of some child care centers and schools to prevent community transmission. When this type of isolation strategy was implemented in the United States, the predicted spread of influenza in communities dramatically slowed. Numerous outbreaks of bacterial and viral infections have commonly been reported in child care centers. In a recent November 2009 report⁶, the CDC described 639 documented infections caused by antibiotic-resistant *Shigella* dysentery originating in daycare centers in northwest Missouri. These bacteria were resistant to both ampicillin and trimethoprim-sulfamethoxazole, the antibiotics most commonly used to treat these microbes, forcing doctors to use antibiotics that are not FDA-

approved for these infections, including the fluoroquinolones, a class of antibiotic that carries a specific caution for cartilage damage in children.

The Role of Vaccinations

As previously detailed, all infants below the age of 2 years are particularly susceptible to bacterial and viral infections due to immature immune systems. Vaccination is one important component of combating the spread and severity of antimicrobial resistant infections.

The AAP has taken pride in being the professional pediatric organization that has for decades developed and promoted an immunization schedule recommended for all children in the United States. Over the past several years, collaboration with the CDC has strengthened the clinical and pharmaceutical science behind the recommendations, building on the careful work of the FDA in its evaluation of the safety and efficacy of each and every vaccine for both children and adults.

The AAP aggressively promotes universal vaccination through its Committee on Infectious Diseases and supports the recommendations of the CDC's Advisory Committee on Immunization Practices for the prevention of the most common and deadly bacterial infections: *Haemophilus influenzae* (meningitis, pneumonia), pneumococcus (meningitis, pneumonia, ear and sinus infections), meningococcus (meningitis) and pertussis (whooping cough), as well as universal immunization to prevent a number of viral infections including influenza and chickenpox.

Increased vaccinations are making a positive difference. Universal protection of children through certain immunizations (protein-conjugated pneumococcal vaccines) has actually decreased antibiotic resistance in the targeted bacteria that continue to circulate in communities. An unexpected but welcome benefit of immunizing infants is the documented decrease in antibiotic-resistant infections in parents and grandparents.

Prior to universal immunization of all infants with vaccines for the most aggressive of these infections, our hospital used to treat over 100 children per year with meningitis, many of whom suffered permanent brain damage. We now treat only about 3 such children each year. However, the few we see are more likely to have an infection with a bacterium resistant to the antibiotics which in the past were capable of successfully treating the infection.

But vaccines alone will not solve this problem in children. There is a critical need for additional vaccines for other types of antibiotic-resistant bacteria, both common and uncommon strains. While the vaccine for pneumococcus that is recommended by the AAP for universal immunization for children has decreased the numbers of children hospitalized with pneumonia and meningitis, it has had far less of an impact on decreasing the number of children with ear infections. Antibiotic-resistance continues to be a problem with ear infections, forcing doctors to use higher dosages of antibiotics and alternative antibiotics to those that were available even 10 years ago.

Perhaps even more frightening is the fact that pneumococcal bacteria continue to evolve under selective pressure from vaccines and antibiotics, and new, antibiotic resistant strains have emerged that now cause extensive, invasive disease across the United States.⁷ New vaccines will hopefully address current issues concerning these new resistant strains, but we are bracing for the evolution of yet newer, resistant bacterial strains. Antibiotic resistance is a moving target, and requires ongoing intense commitments to develop better surveillance tools, better vaccines, and better antibiotics.

Efforts to Promote Appropriate and Judicious Use of Antibiotics

Approximately three quarters of all outpatient prescriptions of antimicrobial agents for children are given for five conditions: otitis media, sinusitis, cough illness/bronchitis, pharyngitis, and nonspecific upper respiratory tract infection (the common cold).

Antimicrobial agents are prescribed, even though many of these illnesses are caused by viruses and are unresponsive to antimicrobial therapy. Physicians report that many patients and parents try to persuade them to dispense unnecessary antimicrobial agents.

As early as January 1998, the American Academy of Pediatrics published, with the CDC, a series of 6 articles in the Academy's official journal, *Pediatrics*, on the Judicious Use of Antimicrobial Agents for Upper Respiratory Tract Infections, in which guidelines were published that challenged the common practice of using antibiotics for sore throats, runny noses and coughs. To minimize the development of antibiotic resistance, pediatricians were urged to use antibiotics only when a true bacterial infection was present, and only for the shortest duration necessary to cure the infection. The AAP Committee on Infectious Diseases continues to promote appropriate use and guidance in their regularly published "Red Book," which is used by pediatricians and many other providers of health care for children.

The AAP, working with their partners including the CDC, has designed and promoted educational materials for pediatricians and for parents. Information that every sore throat does not need to be treated with antibiotics represented a significant challenge to pediatricians who every day face countless sick children and their concerned parents, and know that the vast majority of these children have viral infections and do not need antibiotics. These patient-oriented materials were designed to be shared with parents in waiting rooms and exam rooms, in order to change the parents' and grandparents' expectations during pediatric clinic visits. The AAP assists pediatricians in their efforts to educate parents so that they do not simply go to another provider who will prescribe antibiotics inappropriately.

Collaborations with Other Professional Organizations

The Academy's members include pediatricians who are trained and certified in the field of infectious diseases. Most of these members are also members of the Infectious Diseases

Society of America (IDSA). Many pediatric members of the IDSA are putting extensive efforts into the IDSA's initiatives that are designed to develop safe and effective new antimicrobial therapy for all ages. Those of us who are pediatricians place a particular emphasis on the safety of new drugs for newborns, infants and children.

AAP also works in close partnership with a wide range of other professional organizations on these issues, including the American Medical Association, American Academy of Family Physicians, the National Association of Pediatric Nurse Practitioners, the American Public Health Association, and many others.

The AAP supports the many and diverse antimicrobial resistance programs within the CDC, National Institutes of Health (NIH), and Food and Drug Administration (FDA), as well as public-private partnerships, global collaboration, and work in the pharmaceutical and diagnostics industries to incentivize the development of new antimicrobial agents (e.g., the IDSA's 10 X '20 Initiative). At the same time that we are creating incentives for the development of new antibiotics, we must create an environment for appropriate use of newly developed agents that will allow for the maximum effects of the new agents over the longest possible period of time. It is not a simple task to create new antimicrobial drugs, and it is our obligation to children that we avoid the inappropriate and possibly harmful use of available antibiotics.

Legislative Opportunities

The AAP supports legislation that will define and limit the spread of antibiotic-resistant organisms. H.R. 2400, the Strategies to Address Antimicrobial Resistance, or STAAR, Act, introduced by Committee member Rep. James Matheson (D-UT) and currently cosponsored by Committee members Reps. Tammy Baldwin (D-WI), Donna Christensen (D-VI), and Gene Green (D-TX) creates a comprehensive strategy to address numerous facets of antimicrobial resistance, and provides a means to prevent the spread of antimicrobial-resistant bacteria. Through the legislation, a newly-created Antimicrobial

Resistance Office (ARO), located in the Department of Health and Human Services, would coordinate and extend the activities of many federal agencies currently involved in these efforts. Further, the STAAR Act provides for input from Advisory Panels from the academic and medical practice community to collaborate with federal officials in creating an effective and realistic program. Importantly, improved data collection on the various uses of all antimicrobials and resistance will be a key feature, allowing both federal officials and the medical community to have the information they need to focus efforts on appropriate use. Many agencies, including the CDC, FDA, and NIH currently are involved in various aspects of these issues, but it is essential to coordinate their efforts and provide them access to new tools to manage resistance more effectively.

The AAP also strongly supports the highly successful Best Pharmaceuticals for Children Act (BPCA). This legislation encourages and incentivizes research on drugs in children that would otherwise not occur. Essential data on the uses of antimicrobials and other drugs for neonates, infants and children have been accumulated through the BPCA, allowing children to receive better health care. As an example, safety studies in children on a particular class of antibiotics (fluoroquinolones), that display the potential for cartilage destruction in juvenile animals, was carried out at the request of the FDA. While these antibiotics are not routinely recommended for use in children, they are used when bacteria are resistant to other antibiotics. The manufacturers had no interest in either studying or marketing these antibiotics to children, due to the risks of toxicity that were apparent to all, and the fact that the pediatric demand for the drugs was relatively small. However, as we do use these antibiotics occasionally in all pediatric age groups, including premature infants, it was critical to assess the safety of these drugs in a systematic way. Following completion of these studies, which are available now on the FDA website, all pediatricians are aware of the potential of these drugs to cause cartilage and tendon injury and can weigh that risk appropriately against the potential benefits of use. The outstanding work of the FDA has focused this incentive program on medical questions of the highest priority for children, resulting in more than three hundred sixty drugs being re-labeled through the BPCA, many of them antibiotics.

Finally, the AAP would be remiss if we did not acknowledge the need to address antibiotic use in animal agriculture as a critical component of reducing antimicrobial resistance. The vast majority of antibiotics produced in the United States are used in livestock, often at subtherapeutic levels to promote growth. Judicious use of antimicrobial agents in humans accounts for roughly half of total antibiotic use in this country. Evidence exists that if we are to truly impact this situation, use of antimicrobial agents in food production must be addressed.⁸ AAP strongly supports passage of H.R. 1549, the Preservation of Antibiotics for Medical Treatment Act, which would place reasonable limits on the veterinary use of antimicrobial drugs that are important in human medicine.

Concluding Thoughts

While increasing antibiotic resistance is a disturbing trend for all, it is especially concerning when considering infant and child populations. There is a growing need for more safe and effective antibiotics and better microbial stewardship.

The American Academy of Pediatrics commends you, Mr. Chairman, for convening this hearing today to bring added attention to the important issues surrounding antimicrobial resistance and the judicious use of antibiotics. The Academy is grateful for the Committee's commitment to child health, and we hope that you will consider us a partner and supporter in your efforts to define and limit the spread of antibiotic resistant organisms, particularly as they impact our children.

I appreciate this opportunity to testify and look forward to your questions.

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- ⁶ Arvelo W, Hinkle CJ, Nguyen TA, Weiser T, Steinmuller N, Khan F, et al. Transmission risk factors and treatment of pediatric shigellosis during a large daycare center-associated outbreak of multidrug resistant *Shigella sonnei*: implications for the management of shigellosis outbreaks among children. *Pediatr Infect Dis J* 2009;28(11):976-80.
- ⁷ Pelton SI, Huot H, Finkelstein JA, Bishop CJ, Hsu KK, Kellenberg J, et al. Emergence of 19A as virulent and multidrug resistant *Pneumococcus* in Massachusetts following universal immunization of infants with pneumococcal conjugate vaccine. *Pediatr Infect Dis J* 2007;26(6):468-72.
- ⁸ Shea, KM. Nontherapeutic Use of Antimicrobial Agents in Animal Agriculture: Implications for Pediatrics. *Pediatrics* 2004;114(3):862-868.

Mr. PALLONE. Dr. Eisenstein.

STATEMENT OF BARRY EISENSTEIN

Dr. EISENSTEIN. Chairman Pallone, Ranking Member Shimkus and members of the subcommittee, thank you for the opportunity to testify on the urgent need to spur greater innovation and accelerate the development of new therapeutics to combat the threat of antimicrobial-resistant bacterial infections. I am Dr. Barry Eisenstein, senior vice president, scientific affairs, at Cubist Pharmaceuticals. Cubist is a biopharmaceutical company headquartered in Lexington, Massachusetts. We currently market Cubicin, also known as daptomycin for injection, a first-line intravenous antibiotic against methicillin-resistant *Staph aureus*, MRSA, and other gram-positive infections as well as *Staph aureus* blood infections. Cubist has a growing pipeline of antibiotic candidates against other resistant and difficult-to-treat infections.

We believe antimicrobial resistance is a public health crisis. You have already received testimony from the CDC, NIH, FDA, BARBA, and today, the IDSA, AMA and AAP combined with numerous independent studies is unanimous in two key points. First, antibiotic resistance is an increasingly severe threat to our public health, and second, that gaps in our therapeutic options are growing rapidly by the month, making it urgent that we develop more drugs, more new drugs to develop resistant infections. We are approaching a crisis point with antibiotic resistance and the lack of new drugs against gram-positive bacteria such as *Staph*, gram-negative bacteria such as *acinetobacter*.

Mr. Chairman, you yourself noted in the subcommittee's last hearing that gram-negative infections have become a significant health issue for many servicemen and servicewomen returning from the Middle East with untreatable infections, so why so few antibiotics in development? There are critical economic disincentives at work that profoundly and adversely impact the willingness of companies and others to pursue cutting-edge antimicrobial R&D. As you have heard, the number of new antibiotics approved by the FDA has decreased by 70 percent since the mid 1980s, and a recent peer review study found only five new antibiotics in the R&D pipeline out of more than 506 in development, less than 1 percent. But proven incentives exist to encourage antimicrobial innovation. Three years ago with your leadership, a provision in FDAAA required FDA to answer whether the Orphan Drug Act could be applied in this matter. Regrettably, the agency concluded that they cannot under the law as written.

Despite this setback, like you, Cubist believes there are still options available. We commend IDSA for their 10 by 20 initiative and we strongly support enactment of H.R. 2400, the STAR Act, but we believe that neither the 10 by 20 nor STAR Act includes provisions that would directly encourage development of new therapeutics. As one of the very few American companies discovering and commercializing novel anti-infectives, we believe that incentives must attract more small, mid-market and large companies into pursuing both human clinical studies and earlier stage research. Congress and the Administration need to correct market failures just as they have already for rare diseases, pediatric drug use and medical

countermeasures. I believe such incentives must include the following: one, enhanced market and data exclusivity for qualified infectious disease products; two, exempt qualified infectious disease products from the pharmaceutical excise tax and 340(b) drug discount expansion enacted in health reform; three, authorize the study and establishment of guaranteed market contracts and other pull market mechanisms as well as the use of other transactions authority by the HHS; four, expand tropical disease priority review vouchers as established under FDAAA to apply to qualified infectious disease products; five, create infectious disease product development grants modeled on FDA's successful orphan product development grants; six, codify the task force on global antimicrobial resistance; and seven, improve access to home infusion antibiotic treatment, especially in the Medicare program.

In conclusion, Mr. Chairman, thank you for the opportunity to testify today. Antimicrobial resistance is a very real threat to public health and one that is only getting worse. I urge Congress to act on the consensus recommendations that I and many others offer as steps toward ensuring the development of the next generation of first-line drugs to combat resistant infections.

[The prepared statement of Dr. Eisenstein follows:]

Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives

Hearing on
“Promoting the Development of Antibiotics
and Ensuring Judicious Use in Humans”

Written Testimony of
Barry I. Eisenstein, M.D.
Senior Vice President, Scientific Affairs
Cubist Pharmaceuticals

June 9, 2010

Chairman Pallone, Ranking Member Shimkus, and Members of the Subcommittee, thank you for the opportunity to testify on the urgent need to spur greater innovation and accelerate the development of new therapeutics to combat the threat of antimicrobial resistant bacterial infections.

I am Dr. Barry Eisenstein, Senior Vice President of Scientific Affairs at Cubist Pharmaceuticals. Cubist is a biopharmaceutical company focused on the research, development and commercialization of pharmaceutical products – especially antibiotics -- that address unmet medical needs in the acute care environment. Headquartered in Lexington, Massachusetts, we currently market CUBICIN® (daptomycin for injection), the first intravenous (IV) antibiotic from a class of anti-infectives called lipopeptides. CUBICIN received FDA approval in 2003 for the treatment of complicated skin and skin structure infections caused by certain susceptible strains of Gram-positive microorganisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). CUBICIN is also approved in the U.S. for the treatment of *S. aureus* bloodstream infections (bacteremia), and is the only IV antibiotic approved for this indication based on the results of a prospective, randomized, controlled registration trial. In the wake of a highly successful launch of CUBICIN, the company has a growing pipeline that includes antibiotic candidates for difficult to treat infections including *Clostridium difficile* and serious Gram-negative infections, including those caused by multi-drug resistant *Pseudomonas aeruginosa*.

As Senior Vice President of Scientific Affairs, I am responsible for leading the efforts at Cubist to understand the medical needs best answered by Cubicin, to interact with leading scientists and health care providers in the United States and elsewhere, and to advise our scientific staff regarding ongoing unmet medical needs in the area of infectious diseases, particularly those due to resistant bacteria. I am trained in internal medicine, infectious diseases, and microbiology. I have been a hospital epidemiologist, chief of an Infectious Diseases division, chair of an academic department of microbiology and immunology, the leader of infectious diseases discovery and clinical development at a major pharmaceutical company, and am presently, in addition to my job at Cubist, Clinical Professor of Medicine at Harvard Medical School, where I teach. I hold or have held leadership positions with the Infectious Diseases

Society of America, the National Foundation for Infectious Diseases, and the American Society for Microbiology, and am currently an editor of the journal, *Antimicrobial Agents and Chemotherapy*. I have been studying antibiotic resistance and treating patients with infectious diseases for over three decades, have edited major textbooks, and published over 100 scholarly articles in the field

Fostering Innovation is an Essential Solution Against Antimicrobial Resistance

Mr. Chairman, I commend you and the Subcommittee for pursuing this important public health issue. You have recently received testimony from the leaders of the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH) and, today, the Food and Drug Administration (FDA), echoing numerous independent studies and reports from organizations like the London School of Economics, Extending the Cure and the Infectious Disease Society of America (IDSA) that concur upon the increasing severity of the threat of antibiotic resistance. I would like commend IDSA, in particular, for their recent launch of the 10x'20 Initiative. The Initiative calls on the U.S. and other governments to partner globally – with public and private entities alike – to develop ten new antibiotics by 2020.

These agencies, experts and think tanks are unanimous: the risks to public health at home and abroad are great and the gaps in our medical preparedness and our therapeutic options are not only substantial, but also growing with every passing month.

We are approaching a “crisis point” with antimicrobial resistance and lack of new therapies against gram positive bacteria such as “staph” and gram negative bacteria such as *Acinetobacter*. Among the gram positive bacteria, the disturbing rates of MRSA and the emergence of vancomycin-resistant enterococci (VRE) increasingly leave infectious disease doctors with few, if any, effective therapies for certain strains of bacterial infection.

Mr. Chairman, you yourself noted in the Subcommittee’s last hearing on this topic that gram negative infections like *Acinetobacter* have been a significant issue for our troops returning from the Middle East. Many servicemen and servicewomen have been inflicted with these infections at alarming rates and are often untreatable¹. A 2006 study found that as many of 89 percent of sample infections were resistant to at least three classes of antibiotics and 15 percent were resistant to all nine antibiotics screened². The *Los Angeles Times* noted that these infections have spread beyond Walter Reed to other military hospitals³.

Overuse and misuse of antibiotics has contributed to the development of resistance and has left hospital shelves increasingly barren of effective antimicrobial therapies.

Three years ago, we encouraged this Subcommittee to ask the FDA whether the incentives available under the Orphan Drug Act, which have so successfully driven innovation against rare diseases, might also be made available to promote development of new antimicrobial drugs. With the leadership of this Subcommittee, a provision of the Food and Drug Administration Amendments Act of 2007 (FDAAA, Pub. L. No. 110-85) was enacted that called on FDA to convene a public meeting and determine whether the Orphan Drug Act could be

applied in this manner. Regrettably, the Agency concluded that they cannot under the law as written.

Two years ago, I testified before your colleagues on the Senate Committee on Health, Education, Labor and Pensions that we are facing a “crisis point” in our medical arsenal against resistant infections. Since then, public and clinical awareness of the threats we face has grown. Government authorities and health care decision-makers have taken some steps to better respond to these threats. The Patient Protection and Affordable Care Act (PPACA, Pub. L. No. 111-148) took marginal steps, addressing the quality of inpatient care and hospital-acquired infections, and creating a modest, short-term incentive called the Qualifying Therapeutic Discovery Project Tax Credit.

But today, Mr. Chairman, I can report that much more remains to be done and the urgency is greater than ever. Congress and the Administration must make additional, specific improvements in federal law and policy before we can achieve greater progress against resistant infections. That is why Cubist strongly supports enactment of H.R.2400, the Strategies to Address Antimicrobial Resistance (STAAR) Act. The STAAR Act would enhance research, improve federal coordination, and expand data collection against the threat of antimicrobial resistance.

But even these steps will not foster innovation and the development of new antimicrobial drugs. The STAAR Act does not include provisions that would directly encourage development of new therapeutics. That is why Congress and the Administration should take immediate additional steps on consensus recommendations that already exist to promote the research and commercialization of new drugs, diagnostics and vaccines against resistant infections. These recommendations, like mine today, are clear, simple and actionable. I urge the Subcommittee to take action on them as soon as possible.

Antimicrobial Resistance: A Public Health Threat

During the last several decades, the prevalence of antimicrobial resistant organisms in U.S. hospitals and medical centers has increased. According to 2002 data from the Centers for Disease Control and Prevention (CDC), more than 1.7 million people acquire bacterial infections in U.S. hospitals each year, and 99,000 die as a result. CDC estimates that up to 70 percent of those bacterial infections are resistant to at least one drug, at a cost of approximately \$5 billion annually¹. A recent study published in the *Journal of the American Medical Association* extrapolated data from nine U.S. communities to estimate that there were 94,360 invasive MRSA infections alone in the U.S. in 2005 which resulted in 18,650 deaths²—to say nothing of the prevalence of other drug resistant infections.

Antimicrobial resistance is increasingly a public health threat: patients who contract a resistant infection require more days of antimicrobial therapy than patients who do not; require more days in the hospital than those who do not; and generally face worse outcomes than those who do not³. We must implement effective measures to combat antimicrobial resistance. Unfortunately, given the rapid evolution of bacteria, development of antibiotic resistance is almost inevitable, thus policy efforts to address antimicrobial resistance must focus on:

- 1) Adoption and maintenance of practices that reduce the rates of transmission of resistant infections;
- 2) Appropriate use of existing antimicrobials to delay development of resistance; and
- 3) Implementation of incentives to encourage the continued research and development of new antimicrobials to ensure, to the extent possible, a steady supply of effective drugs.

Lack of Effective Antimicrobials is Reaching a Crisis Point

As a class of drugs, antibiotics face unique therapeutic challenges, which other treatments do not encounter. Bacteria evolve so quickly that development of resistance is inevitable and thus each new antibiotic is a “wasting asset” with a finite period of time during which it will be effective. For example, the discovery of penicillin in 1928 was nothing short of a medical miracle. Yet only four years after the drug became widely commercially available during World War II, reports of resistant microbes began emerging. This has far reaching consequences for patients and physicians who may be left without therapeutic options, but it also profoundly and adversely impacts the willingness of industry to invest in antimicrobial R&D as newer agents effective against the most important antibiotic-resistant pathogens, like MRSA, are often viewed as niche products to be used highly selectively by practicing physicians.

Industry’s reluctance to invest in antimicrobial development is compounded by the depreciating nature of antimicrobials—when faced with the reality that antibiotics have a finite lifespan, health care providers engage in the practice of optimizing antibiotic utilization (“antibiotic stewardship”). While this can result in more appropriate use of antimicrobials (e.g., prescribing antibiotics only when necessary, effectively using diagnostic techniques to select the most appropriate antibiotic, and acquiring appropriate culture and sensitivity data to ensure suitable dosing), it can also result in physicians simply reserving the newest antibiotics for use only as a last resort in the most difficult-to-treat cases⁴.

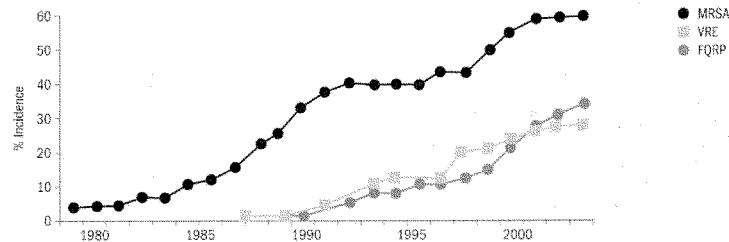
Yet this appropriate goal of preserving antibiotics paradoxically hurts the “supply side” of a pharmaceutical manufacturer’s potential market by making commercial return on these antibiotics more difficult to realize. This is a critical economic disincentive for industry to engage in cutting edge antimicrobial R&D. The consequence is loss rather than gain in the antibiotics armamentarium, a fact not well appreciated by practicing physicians or by some proponents of antibiotic stewardship⁴.

Finally, antimicrobials are used in acute settings, for limited timeframes (7-10 days), rather than daily for the life-time of the patient, as with treatments for chronic diseases, making it even more difficult to rely on commercialization of an antimicrobial as a steady source of financial returns. In addition to challenges inherent to antibiotics as a class of drugs (emergence of resistance, prescribing habits, and resulting antimicrobial stewardship), over the last decade, regulatory uncertainty, including ever-shifting FDA guidelines has had a significant negative impact on approval of antibiotics. According to *Extending the Cure*, 14 classes of antibiotics were introduced for human use between 1935 and 1968; since then only five have been introduced⁴. While many factors, as discussed above, have contributed to this decline,

unpredictable approval requirements and timelines only add to already existing economic disincentives for industry to invest in antimicrobial R&D¹⁰.

These well-documented features of the antimicrobial market are identified time and again by economists, analysts, and independent think tanks as the reasons why both big and small pharmaceuticals and biotechnology companies have largely fled from R&D investment in anti-infectives, preferring instead to focus on other, more financially certain therapeutic areas. A recent analysis published in *Clinical Infectious Diseases* (CID) found only five new antibiotics in the R&D pipeline out of more than 506 drugs in development. By comparison, pharmaceutical companies were developing 67 new drugs for cancer, 33 for inflammation/pain, 34 for metabolic/endocrine disorders, and 32 for pulmonary disease. The CID analysis found that FDA approvals of new antibiotics declined 56 percent during the past 20 years (1998-2002 versus 1983-1987). The consequences of this lack of antimicrobial R&D have become devastating for patients, leaving us with increasing rates of antimicrobial resistance and fewer and fewer available therapies¹¹.

Figure 1. The emergence of antimicrobial-resistant bacteria over time¹².



MRSA=methicillin-resistant *Staphylococcus aureus*; VRE=vancomycin-resistant enterococci; FQRP=fluoroquinolone-resistant *Pseudomonas aeruginosa*.

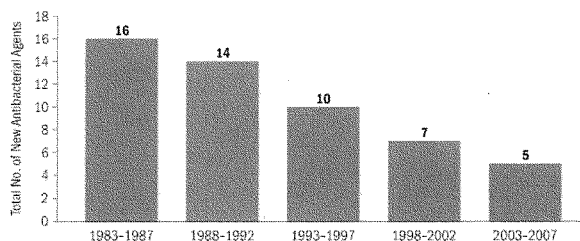


Figure 2. FDA approval of new antibiotics has decreased by 70% since the mid-1980s¹².

Proven Incentives Exist to Encourage Antimicrobial Innovation

As one of the few American biopharmaceutical companies primarily focused on the discovery and commercialization of novel anti-infectives, Cubist has unique insight into the market and regulatory barriers to innovative antimicrobial research and development. We believe that specific policies that have worked successfully to correct similar market failures in rare diseases, pediatric drug use, and medical countermeasures, can and should be applied by Congress and the Administration to the “dry pipeline” of antibiotics and antimicrobials.

We believe it is critical that Congress consider policies that will not only help sustain companies like Cubist already engaged in the full spectrum of drug discovery, from molecular discovery to animal studies through complex, multicenter pivotal human trials, but also attract new entrants – large and small – into this critical therapeutic area. We urge you to keep in mind the high risks, extraordinary expense, and unpredictability of the research and development that are entailed in bringing a new antibiotic to market. For these reasons, new incentives must be designed so that they encourage investment in activities across the research spectrum, from basic research to clinical trials, and target as broad a range of scientists, entrepreneurs, large and small companies, and life science investors as possible.

With these thoughts in mind, Cubist respectfully recommends consideration of the following options, in order of their importance and potential beneficial impact:

(1) Enhance market and data exclusivity for qualified infectious disease products.

In the past, Congress has successfully corrected other pharmaceutical market failures and promoted robust innovation through extensions of exclusivity. Tremendous progress has been achieved in reversing the absence of investment and R&D in rare diseases through the Orphan Drug Act, as well as the pediatric uses of medicines through the availability of 6-month pediatric exclusivity. As I mentioned earlier, this Subcommittee and Congress recently explored the possibility of applying Orphan Drug Act exclusivity to novel antimicrobials. Applying this proven, effective incentive to this narrow and well-documented market failure would send a

strong signal to scientists, entrepreneurs, venture capitalists, and the markets, and greatly encourage more R&D and commercialization of new drugs to treat resistant infections.

Recognizing that our greatest concern must be to foster and maintain effective treatments against resistant infections in humans (and not in animals), I encourage the Subcommittee to consider linking any extension of exclusivity for novel antimicrobials to an assurance that the qualified novel agent be prescribed responsibly for human use only.

(2) Exempt qualified infectious disease products from the pharmaceutical excise tax and 340B drug discount expansion enacted under PPACA.

Under PPACA, pharmaceutical manufacturers are required to pay an excise tax based upon a sliding scale of branded prescription drug sales for the preceding calendar year, in proportion to the relevant sales of all manufacturers. Yet Congress exempted orphan drugs from these calculations to maintain, as much as possible, the financial incentives to pursue development of these important therapeutics. Similarly, PPACA expands the scope of covered entities eligible for drug discounts on the purchase of outpatient drugs available under section 340B of the Public Health Service Act, but also exempts drugs with orphan designations from the FDA from this expansion for the newly eligible covered entities. Expanding these limited exemptions from the excise tax and the 340B discount expansion to qualifying infectious disease products would create highly visible financial incentives to pursue their development.

(3) Authorize the study and establishment of guaranteed market contracts and other “pull” market mechanisms, as well as the use of “other transactions” authority of HHS.

Last year, the London School of Economics published a report on incentives to promote innovation in antimicrobial therapeutics. The report was commissioned by the Swedish government in its capacity of the European Union Presidency. Among those incentives studied were market “pull” mechanisms, such as monetary prizes and advance market commitments, which serve as general incentives to drug development, encouraging pre-clinical and clinical development through a pre-commitment of donors to buy an effective antimicrobial if and when it is actually developed, and when its efficacy is established and confirmed by an appropriate regulatory authority. Additionally, under 10 U.S.C. § 2371, the Department of Defense (DoD) employs statutory authority to develop highly flexible “other transactions” contractual instruments that are different from procurement contracts, grants, cooperative agreements, and cooperative research and development agreements (“CRADAs”).

We believe these authorities, which are among those exercised by the Department of Health and Human Services (HHS) and its Biomedical Advance Research and Development Authority (BARDA) for the purpose of encouraging the development of medical countermeasures, are readily applicable to unmet needs in the area of antimicrobials.

(4) Expand tropical disease priority review vouchers, as established under FDAAA, to apply to qualified infectious disease products.

Section 1102 of the FDAAA authorizes FDA to award priority review vouchers to sponsors of certain tropical disease product applications; a priority review is a review conducted with a goal date of 6 months. A priority review voucher may be used by the sponsor who obtains it, or may be transferred from the sponsor (including by sale) to another sponsor of a human drug application. This policy is intended to create a positive, 'tradeable' incentive to encourage companies to pursue drug development in neglected global diseases and could be easily expanded to the development of priority antimicrobials.

(5) Create infectious disease product development grants modeled on FDA's successful orphan product development (OPD) grants.

Like the 7-years of market exclusivity authorized under the Orphan Drug Act, orphan development grants administered by FDA successfully encourage the clinical development of products for use in rare diseases or conditions. Congress could authorize grants modeled on this successful program specifically directed at antimicrobials and other infectious disease products. Like the orphan product grants, grants for infectious disease product development would focus targeted federal dollars in an area of critical public health need but limited commercial potential.

(6) Codify the task force on global antimicrobial resistance.

In November 2009, the EU and the U.S. agreed to establish a transatlantic task force to address antibiotic resistance. Under the U.S./EU agreement, the Task Force will focus on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs. Congress should codify the task force and expand its focus beyond transatlantic antimicrobial resistance. The task force could expand upon, or complement, the current federal Interagency Task Force on Antimicrobial Resistance.

(7) Improved access to home infusion antibiotic treatment especially in the Medicare program.

Medicare is the one health care program that fails to cover home infusion services in the traditional fee-for-service – or Part B – arena. All other major health insurers as well as Medicare Advantage plans provide coverage for antibiotics infused in the home setting. Home infusion coverage would allow patients in need of antibiotic treatment -- including those with MRSA or other resistant bacterial infections to receive the drugs they need at home in a non-hospital setting. Not only is home-based care easier for the patient, but keeping these patients out of the hospital would help reduce the spread of such resistant infections in acute care setting.

I'd like to thank Congressman Engel for his leadership in seeking to include in the recently enacted health care reform law changes to Medicare that would provide for home infusion services. While this change was not included in the law as enacted, this lack of

Medicare coverage and other reimbursement challenges remain part of the larger equation of incentives that must be addressed in order to draw more companies, researchers, and investors into this space.

Conclusion

Mr. Chairman, thank you for the opportunity to testify today. Antimicrobial resistance is a very real threat to public health and one that is only getting worse. I urge Congress to act on the consensus recommendations that I, and many others, have offered as steps towards assuring the development of the next generations of first-line drugs to combat resistant infections, as well as managing the emergence, transmission, and treatment of drug resistant organisms.

Endnotes

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- ⁹ See, *Extending the Cure, Policy Responses to the Growing Threat of Antibiotic Resistance, Policy Brief 6: The Antibiotic Pipeline*, May 2008, available at http://www.extendingthecure.org/downloads/policy_briefs/Policy_Brief6_May08_newdrugs.pdf.
- ¹⁰ See, Docket No. FDA-2008-N-0225-008.1 and -008.2, Comments of the Infectious Diseases Society of America, available at <http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2008-N-0225>.
- ¹¹ See, *Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates...A Public Health Crisis Brews*, Infectious Diseases Society of America, July 2004, available at <http://www.idsociety.org/WorkArea/showcontent.aspx?id=5554>; G.H. Talbot et al., *Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America*, Clinical Infectious Diseases, 2006;42:657-668; B. Spellberg et al., *The Epidemic of Antibiotic Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America*, Clinical Infectious Diseases 2006;42:155-164.
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Mr. PALLONE. Thank you, Dr. Eisenstein.
Dr. Levi.

STATEMENT OF JEFFREY LEVI

Mr. LEVI. Thank you, Mr. Chairman, thank you, Ranking Member Shimkus. I am Jeff Levi. I am the executive director of Trust for America's Health. We are a not-for-profit non-partisan public health advocacy organization.

Antimicrobial resistance, or AMR, is not an abstract concern. As we have heard, we live in a world where antibiotic resistance is believed to be responsible for over 90,000 deaths a year in the United States. That is more than die of diabetes or Alzheimer's or HIV. And AMR poses a totally unnecessary burden on the U.S. health care system.

We face this problem in part because the market has failed to meet the need for new antimicrobials. In my oral testimony, I am going to focus on the primary research and development questions that I think we need to address this market failure, but my written testimony discusses two other critical components to this effort, and that is federal leadership and prevention, and I would like to briefly comment on those first.

First, the Administration has taken a major step forward in creating new locus for leadership regarding AMR by establishing the new position of deputy assistant secretary for health and infectious diseases. This new leadership, we hope, will provide the development and oversee the updated public health action plan to combat antimicrobial resistance and that will be a robust and comprehensive plan that addresses the many issues outlined in the testimony you are hearing today.

Until we develop new antimicrobial agents, we must depend on prevention. While much has been started, we hope that the Administration will embrace a far more aggressive national education campaign about appropriate use of antimicrobials and non-pharmaceutical approaches to prevent transmission of resistant bacteria. Above all, we hope the Administration will step back from its proposed cut of \$8.6 million in funding for State and local health departments to track and control antibiotic resistance.

Ultimately, the problem of antimicrobial resistance will not be resolved until we have better diagnostics, new antimicrobial agents and new vaccines, but few new products are in the pipeline, as we have heard. This is primarily because the market has failed. We need to change that equation. To date, the largest federal investment in creating market incentives is through BARDA. Unfortunately, while BARDA has the authority to do the research we need to do, it is chronically underfunded. Even the proposed \$476 million for fiscal 2011 for BARDA is a fraction of what BARDA needs to incentive development of a range of countermeasures, not just antimicrobials. With scarce funding the federal government has been unable to demonstrate to industry that they will be full partners. The existing options beyond BARDA including potential expansion of the Orphan Drug Act, prioritization of vouchers for companies that focus on neglected tropical diseases and advanced purchase arrangements are all necessary but we believe probably insufficient to create the research and manufacturing capacity and/

or the demand for developing new antimicrobial agents. These financial and regulatory incentives may continue to attract small companies but we worry that they will not attract the larger companies with the manufacturing and marketing capacity to bring new antimicrobial products to scale.

Even if we successfully address the market issues, we still need policies and programs that will also create the intellectual capital in the academic and private sector-based biomedical research community if we are to answer the range of basic research questions and then develop new products.

In short, I think we are left with more questions than answers, and so we need a collaborative effort between the private sector and the public sector, and I hope it will be reflected in the forthcoming action plan and that it can address some of the following questions. What is the right mix of direct financial incentives and regulatory protections to bring new companies to the table? What policies and incentives can the government create that will result in a willingness of venture capital to invest in development of new antimicrobial agents? Government financing a loan does not need to be the answer. We have begun to see venture capital play a new role in development of new influenza-related products and we learn from this experience and bring more players to the table. What investments does the NIH need to make to incentivize biomedical researchers to re-engage with the field of antimicrobial development so they see a long-term future in this field? What policies can FDA put in place in advance so that potential investors in research know the pathway to approval? And finally, and just as important, what policy and financial arrangements will assure that new products developed with special federal financial support or regulatory incentives will be accessible and affordable to domestic consumers reflecting the taxpayers' early investment in their development? Any plan should come with a professional judgment budget so that the Congress and the Administration can make appropriate estimates of the potential return on an increased federal investment. If the HHS plan fails to address these issues properly, an independent entity should be empowered to develop that plan.

AMR is a solvable problem if we are creative enough in our policies and our investment strategies. As the bugs adapt, so must we.

Thank you again for the opportunity to share our views today.
[The prepared statement of Mr. Levi follows:]

**House Committee on Energy & Commerce
Subcommittee on Health
Hearing on “Promoting the Development of Antibiotics and
Ensuring Judicious Use In Humans”
Testimony of Jeffrey Levi, Ph.D.
Executive Director, Trust for America’s Health
June 9, 2010**

Thank you, Mr. Chairman. I would like to commend you for holding this timely and important hearing. My name is Dr. Jeffrey Levi and I am the Executive Director of Trust for America’s Health, or TFAH, a nonprofit, nonpartisan public health advocacy organization dedicated to saving lives by working to make disease prevention a national priority. I appreciate the opportunity to testify before you today to discuss an ongoing public health crisis, the growing resistance of microbes to existing antibiotics.

This is a problem that has concerned our organization for some time. In fact, this critical issue was highlighted in our 2008 report, *Germs Go Global: Why Emerging Infectious Diseases are a Threat to America*,¹ which found that the growing rise and spread of antimicrobial resistance (AMR) has led to the development of resistant pathogens and allowed many diseases formerly treatable with drugs to resurge and take hold with new vigor. I ask that a copy of this report be included in the hearing record.

As you know, antibiotics are one of the greatest public health developments of the past 70 years. However, nature and biology keep challenging our biggest accomplishments. In your April 28th hearing, Dr. Thomas Frieden, the director of the Centers for Disease Control and Prevention (CDC), summed up the challenge before us very well. He stated that we are headed toward a “post-antibiotic world in which we have few or no clinical interventions for some infections.”

This is not an abstract concern. We are already living in a world where antibiotic resistance is believed to be responsible for over 90,000 deaths a year in the United States. That’s more than die of diabetes or Alzheimer’s or HIV. This comes at a great human toll and poses a totally unnecessary burden on the U.S. health care system. The CDC estimates that the health care costs associated with AMR range from \$28 billion to \$45 billion² -- money that could be saved by public and private insurance plans. Yet, we have not made the level of investment needed to address this crisis.

Despite the size of the problem, AMR has not attracted private sector interest and investment on the scale of other biomedical challenges. When there is market failure to address a major public health concern, it becomes incumbent upon the government to

¹ Also available from: <http://healthvamericans.org/report/56/germs-go-global>

² Scott, R. Douglas, “The Direct Medical Costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention,” Centers for Disease Control and Prevention, March 2009. http://www.cdc.gov/ncidod/dhqp/pdf/Scott_CostPaper.pdf

create the climate and, if need be, provide the resources, to address this challenge. And that requires a multi-faceted approach that includes:

- Leadership by the federal government at a level that recognizes that this is a public health problem that requires immediate national and international attention and requires setting ambitious, but achievable goals if we are committed – such as the 10 by 20 goal of bringing to market 10 new antimicrobials by the year 2020;
- Prevention campaigns, policies, and strategies that assure prudent use of existing antimicrobial agents and reduce transmission of drug-resistant strains; and
- Research and development that creates the incentives for the best minds and the most successful companies to invest their talents and their capital in finding new diagnostics and new antimicrobial agents.

I will now address each of these elements in turn, but let me emphasize one very important overarching point. In the current situation, the burden of antimicrobial resistance is borne by the health care system and by consumers --- paying the price in avoidable death, illness, and health care costs. That needs to change.

Leadership

Successful response to AMR requires leadership at the federal level. The proposed Strategies to Address Antimicrobial Resistance (STAAR) Act identifies the key elements of the federal response: a government-wide strategic plan, a comprehensive research agenda, and increased coordination among the federal agencies with roles to play in AMR response. We are pleased to see that the Administration has not waited for passage of the STAAR Act to begin to address its goals in several ways.

The recent appointment of Dr. Ronald Valdiserri to the newly created position of Deputy Assistant Secretary for Health, Infectious Diseases, creates a locus for leadership for a cross-governmental AMR strategy. Prior to this appointment, there was no official in charge of coordinating infectious disease policy across the agency.³ We also look forward to the updated Public Health Action Plan to Combat Antimicrobial Resistance and hope that this strategy will be coordinated with other efforts, including the forthcoming medical countermeasures strategy being developed by the Assistant Secretary for Preparedness and Response. We also hope that there will be recognition on the part of the Administration – both through the work of ASPR and through engagement of the National Security Staff at the White House – that AMR is not just a traditional public health threat, but one that has serious bioterrorist potential as well.

Because of this twin threat – the health care challenges of AMR and the potential for weaponizing AMR – strategies and plans will not suffice. We will need the Administration and Congress to empower the relevant federal agencies to carry out their strategies by giving them the financial resources they need. This is particularly important

³ “Health-Care-Associated Infections in Hospitals: Leadership Needed from HHS to Prioritize Prevention Practices and Improve Data on These Infections,” GAO-08-673T April 16, 2008.

in the area of research and development, which I will discuss later, where we are only providing a fraction of what is needed. Strategies without resources are pieces of paper that give false hope to those at risk to AMR-related conditions.

Prevention

Development of new antimicrobial agents will take time. However, we are not without options in containing the spread of antimicrobial resistance. We have at our disposal prevention strategies that can achieve two critical goals – we can reduce the spread of new infections through appropriate infection control, and we can reduce development of further resistance through the more prudent use of antibiotics.

Addressing AMR must be a central part of the new national effort to ensure health care quality. HHS should make maximum use of its new authorities under health reform to combat this problem. Everyone in our country has the right to expect that health care acquired infections (HAIs) should be “never” events. We applaud the steps already taken by the Center for Medicare and Medicaid Services (CMS) to end reimbursement for HAIs, and are pleased that many private payers are following suit. This provides hospitals the incentive to lower infection rates.

CMS also includes some measures of appropriate antibiotics use in its Annual Payment Update database, where hospitals report certain quality measures.⁴ CMS could implement tracking of prudent use of antimicrobials, as it does for HAIs, and withhold reimbursement for providers and facilities that regularly inappropriately prescribe. Health IT could be an important mechanism for HHS to track use, if appropriate antimicrobial prescribing is included as a quality measure under the regulations for meaningful use of electronic health records.

Consumers also have a responsibility in fighting AMR. We are pleased that the CDC is expanding its Smart Use campaign to educate consumers about prudent use of antibiotics. We hope that sufficient resources can be identified to assure that this is truly a national education campaign. If consumers learn when they may need antibiotics and when to avoid them, providers are likely to feel less pressure to inappropriately prescribe.

Consumers should also be educated about and empowered to demand non-pharmaceutical protections in the health care setting, such as hand-washing and glove wearing. Health professions and public health associations and schools should similarly educate their constituencies on the prudent use of antibiotics and provide them with the necessary tools to say no to patients who request antibiotics for non-bacterial infections.

That said, the President’s FY 2011 proposed budget for prevention does not reflect the severity of the problem. Indeed, the proposed budget cuts the CDC’s prevention and

⁴ GAO, 2008.

education efforts by \$8.6 million, which would decrease the number of health departments receiving grants to track and control antibiotic resistance from 48 to 20.⁵

We recommend that this committee ask CDC for a professional judgment budget that would define the resources needed to support federal, state, and local efforts as well as to support a national campaign addressing both sides of the AMR equation: prudent use and consumer empowerment about non-pharmaceutical protections. Under the health reform law, Congress has authorized, and the Prevention and Public Health Fund has the resources to support, a national prevention campaign. This would be an excellent focus for part of that campaign.

Research and Development of New Products

Ultimately, the problem of antimicrobial resistance will not be resolved until we have better diagnostics, new antimicrobial agents, and new vaccines to prevent the diseases that are associated with resistance. But few new products are in the pipeline – certainly nothing on the scale reflected in the Infectious Diseases Society’s 10 by 20 campaign. This is primarily because the market has failed: there are insufficient financial incentives for industry or academia to divert their current research and development efforts from more profitable enterprises. We need to change that equation.

To date, the largest federal investment in creating incentives is through the Biomedical Advanced Research and Development Authority (BARDA), and we are pleased to see them at the hearing today. Unfortunately, their programs are chronically underfunded. BARDA’s FY 2010 funding is \$341 million, with \$476 million requested by the President in FY 2011. But even with the proposed FY 2011 increase, this does not come close to what BARDA needs to incentivize development of a range of countermeasures, not just antimicrobials. Indeed, the Center for Biosecurity has estimated that BARDA would need \$3.39 billion to have a 90 percent chance of successfully developing medical countermeasures identified in HHS’ Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Implementation Plan.⁶

With scarce funding, the federal government has been unable to demonstrate to industry that they will be full partners in developing and procuring new antimicrobials. We have seen that small pharmaceutical companies are more willing to contract with BARDA. Larger companies see a bigger return on investment for pharmaceuticals to treat chronic disease than for new medical countermeasures. However, due to their size, these small companies assume tremendous risk to their survival if contracts fall through, so predictability of funding is key to maintaining private sector involvement.

⁵ Department of Health and Human Services, “Fiscal Year 2011: Centers for Disease Control and Prevention, Justification of Estimates for Appropriation Committees,” p. 111.
http://www.cdc.gov/fmo/topic/BudgetInformation/appropriations_budget_form_pdf/FY2011_CDC_CJ_Final.pdf

⁶ Center for Biosecurity of UPMC, “Center for Biosecurity Recommendations for BARDA Funding for FY 2009,” March 31, 2008. Available from: http://www.upmc-biosecurity.org/website/resources/commentary/2008-03-31-barda_funding_fy09_burr.html

The existing options beyond BARDA – including potential expansion of the Orphan Drug Act, prioritization vouchers for companies that focus on neglected tropical diseases, and advance purchase arrangements – are all necessary but, we believe, probably insufficient to create the research and manufacturing capacity and/or the demand for developing new antimicrobial agents. These financial and regulatory incentives may continue to attract small companies, but we worry that they will not attract the larger companies with the manufacturing and marketing capacity to bring new products to scale. Existing protections under the Orphan Drug Act are relatively generous. But they have not brought broad investment in antibiotics. We believe it is unknown whether extended exclusivity would change the equation. On the one hand, these are new drugs that may have a short lifespan if resistance develops, and so extended exclusivity may not reduce the risk for the investor. On the other hand, if the new drug is truly one that overcomes the problem of resistance, then the market should be large enough to draw in industry without additional exclusivity.

Even if we successfully address the market issues, we still face a major challenge: we need a comprehensive approach that will also create the intellectual capital in the academic-based biomedical research community – along with interest in the major pharmaceutical and biotech companies – to answer the range of basic research questions and then develop the diagnostics, treatments, and vaccines that will effectively prevent or treat AMR.

Given the combined public health and bioterrorist threat associated with AMR, we hope that the forthcoming Public Health Action Plan to Combat Antimicrobial Resistance will include a national plan that defines in a comprehensive way the appropriate role, and new incentives needed, for the key players who can resolve this problem:

- What is the right mix of direct financial incentives and regulatory protections such as extended market exclusivity to bring new companies to the table?
- What policies and incentives can the government create that will result in a willingness of venture capital to invest in development of new antimicrobial agents? Government financing alone does not need to be the answer. We saw the beginning of venture capital playing a role in development of new influenza-related products. Can we learn from this experience and bring more players to the table? Similarly, can we learn from the experience of other government agencies, such as the CIA, which has chartered a venture capital fund (In-Q-Tel) to foster commercial development of IT products that would serve the CIA's strategic needs?⁷ In-Q-Tel is an outside entity that brings together industry, academia, venture capitalists, and others to foster the development of new technologies.⁸ This model has been successful because of robust government funding, strategic investments, and the opportunity for profit for other venture capitalists.

⁷ In-Q-Tel, History, Available from: <http://www.iqt.org/about-iqt/history.html>.

⁸ Yanuzzi, Rick, "In-Q-Tel: A New Partnership Between the CIA and the Private Sector," *Defense Intelligence Journal*, CIA, 2000. Available from: <https://www.cia.gov/library/publications/additional-publications/in-q-tel/index.html#snapshot>

- What policies and incentives – beyond those in place today – can bring larger pharmaceutical and biotech companies to join in the research and development effort?
- What investments does the NIH need to make to incentivize biomedical researchers to re-engage with the field of antimicrobial development? This needs to go beyond traditional support for specific research efforts so that individual researchers and institutions see a long-term future in this field.
- What policies can FDA put in place in advance so that potential investors in research know the pathway to approval?
- What basic research do NIH and CDC need to conduct to provide the intellectual base for industry investment in new products?
- And just as important, what policy and financial arrangements will assure that new products developed with special federal financial support or regulatory incentives such as extended patent exclusivity will be accessible and affordable to domestic consumers, reflecting the taxpayers' early investment in their development? We also need to assure that these products are available globally.

Any plan should come with a professional judgment budget – estimating what the public sector costs of this plan would be and what level of investment from the private sector can reasonably be incentivized – so that Congress and the Administration can make appropriate estimates of the potential return on an increased federal investment.

If the HHS plan fails to address these issues properly, we would urge Congress to require that a contract with an independent entity – which is empowered to bring all the relevant stakeholders to the table: government, industry, academia, and consumer representatives – to develop such a plan.

Conclusion

Antimicrobial resistance is both a public health and a national security threat. It is causing unnecessary death and illness – some that can be prevented with existing capacities and some that will require new authorities and funding. But it is a solvable problem – if we are creative enough in our policies and our investment strategies. As the bugs adapt, so must we.

Thank you again for the opportunity to share our views today. I look forward to any questions you and members of the committee may have.

Mr. PALLONE. Thank you, Dr. Levi. Let me thank all of you. As you know, we are going to take questions now, and I will start with myself.

Some of you mentioned that antibiotics are unique among drugs because the more they are used, they less effective they become, so in order to preserve their effectiveness, they need to be used infrequently. That is a very different situation from drugs used, for example, to treat a rare cancer. Yet even with these differences, a couple of you suggested that we should look at extending the market exclusivity provided to antibiotics like we did with the Orphan Drug Act and exclusivity, of course, delays generic competition and deprives patients and the overall health care system of the critical savings they provide. You know, we are always worried about saving money around here. So if we are going to consider this kind of incentive, we need to have every confidence that it is justified and it will work. So let me ask those of you who addressed this, beginning with Dr. Eisenstein, if you can explain how adding 6 months or even 2 years of exclusive marketing would result in companies investing in antibiotic development when, as I mentioned, the only way to preserve an antibiotic's effectiveness is to minimize its use. You understand, it seems a little disingenuous. In other words, during the period of exclusive marketing, the public health goal would be to minimize use of the drug and thus minimize its sale. So under those circumstances, why would additional market exclusivity be a successful inducement for antibiotic development? I am confused. How do you juxtapose those two?

Dr. EISENSTEIN. I think you are talking about really two answers to the same problem, the problem that we have today about antibiotic resistance, and I am not an economist, but as has been explained to me from smart economists who have looked at this, there is an issue of supply and an issue of demand. The issues of demand have been very well discussed by the panelists here today, I believe, in terms of things like antimicrobial stewardship, which by the way I as a physician working at a pharmaceutical company strongly subscribe to and agree with. What this means is that a given company like Cubist would actually forego profits that it might otherwise be able to get if it were not selling antimicrobials, if it were selling some other product. So make up for that, because of the otherwise perverse aspects that controlling the demand side is perversely then hurting the supply side by providing an extra disincentive, you give back to the company extra time to regain the investment that they have made previously, albeit in several more years out.

Mr. PALLONE. Right, but I guess what I am——

Dr. EISENSTEIN. Albeit, it is not at the same level.

Mr. PALLONE. Maybe you have answered this but maybe I don't understand. I understand that, but, I mean, what about this other factor which is that you have this health goal to minimize use of a drug and doesn't that mean minimize its sale? So how do you address that in the context of the market exclusivity?

Dr. EISENSTEIN. Well, again, market exclusivity would provide the innovative company with a longer launch pad.

Mr. PALLONE. So the fact that they were trying to minimize use as a public health goal wouldn't be significant because you have a longer period of time?

Dr. EISENSTEIN. It would tend to balance that out, and that is how you give back for the degree of control at the front end.

Mr. PALLONE. All right. I want to ask two more and I am going to be quick here. Dr. Spellberg, you think 15 to 20 years of exclusivity is necessary. Now, that far exceeds any other terms of market protection that we have in place today, so why do you give it such a long period? Unless I misunderstood, I thought you said 15 to 20 years.

Dr. SPELLBERG. So from my understanding, the current orphan drug, if you can apply the orphan drug to a product for 7 years.

Mr. PALLONE. Yes, and we have others. In health care reform, we did for generic follow-up biologics, I think that was 14 or maybe 12. But you are at 15 to 20.

Dr. SPELLBERG. Well, I think this was just a concept that we are in really bad shape with antibiotics and we have to do something potent to fix it, and I think one of the really important central concepts that IDSA believes is that there isn't going to be one incentive that fixes this problem, there is going to be a panel of them, and whatever panel is felt to be most fiscally responsible and effective is fine.

Mr. PALLONE. So it is one of the pieces?

Dr. SPELLBERG. Exactly.

Mr. PALLONE. And that is sort of what Dr. Levi says, so I will end with you. You expressed skepticism about whether exclusivity would work, and I think you did give us a whole panoply, so just give me a little more information about why you have questions on exclusivity and how important that is by comparison to some of the other things you mentioned.

Mr. LEVI. I am not sure I know the answer to what is the right balance.

Mr. PALLONE. I know. None of us do. But I would like your opinion.

Mr. LEVI. But I think market exclusivity plays a role but I think we are not entirely clear about how major a role, how much of an incentive it is going to be, and I think we have this very strange situation where on the one hand we want to discourage use, which even with some additional exclusivity, will that be enough to bring big manufacturers to the table, and that is what we really need. We need both the intellectual capital that these big companies have and the production and marketing capacity that they have. If it is dramatically successful and becomes a new major antibiotic, we wouldn't necessarily—we want prudent use but it may then have a very large market that goes beyond what was ever intended in the Orphan Drug Act. So I think we have to try to figure out what that right balance is, and I guess I have to come back to my bottom line as to why all these questions still remain is that we haven't invested the money that it is going to take and a lot of this is going to take federal dollars, and we have the authority in agencies like BARDA to promote this development and I think industry feels this is a much improved process but we haven't put enough resources into it. We put a fraction of the resources into to even de-

velop the products that are already on the agenda that BARDA has and so it is going to take a significant mix.

Just one last thought, which is, once we make those federal investments, we need to make sure that these are indeed accessible to consumers and that the federal government doesn't pay twice so that I would suggest that the 340(b) program is actually very important. If we are subsidizing care for people, whether it is through Medicaid or the community health centers, if the federal government is paying for the direct care, we shouldn't be paying for it twice if we have already invested in the development of those products.

Mr. PALLONE. All right. Thank you.

Mr. Shimkus.

Mr. SHIMKUS. Wow, so many questions, so little time, all the doctors at the table. I have learned a couple things from listening to the testimony and perusing. This is serious business, and I just don't know if we are serious about it yet. So I think you are helpful in the testimony. Some of you like the STAR Act and the STAR man is here, so I am going to talk with him about it, but also some of you said it is not enough, so there is probably some building that has to be done and I look forward to working with Congressman Matheson, who is a good friend and an honest broker, which I think you need in this business.

Dr. Levi, I'm just making comments and I am going to try to get to questions, but you mentioned market failure, and I think the charts in both testimonies shows that we don't have, and I don't know if Dr. Woodcock mentioned the small little uptick, if this was really just Pollyannaish or, you know, trying to feed up some optimism based upon FDA, but I think there needs to be a discussion of market failure or government failure, that there may be both here, and that is where I want to encourage you all to continue to talk. If we really believe that there is a serious problem, we can get to a solution but we all have to be working together and we will develop a consensus, and so I think there is hope for that because we have had successes in marketing new drugs from pediatric exclusivity to other things, what we have done on the biologics, and we have done this stuff. So there are things that we can do.

I have stayed off beating up my friends on the new health care law and also some panelists here, so my intent is not to do that, but I do think, Dr. Eisenstein, you did mention the excise tax on pharmaceuticals in your testimony. One of your solutions is, we need to get relief from that as an incentive, which if you then go on to take it to its natural conclusion, which means that the excise tax must be an inhibitor to certainty or return on investment or something to the pharmaceutical practices, which also was mentioned that President's fiscal year 2011 \$8.6 million cut in preventive and education, which I think a lot of people don't talk about it, or was highlighted in the last panel also was if we want to move people off antibiotics, we want to move them to—and this was Congressman Murphy's point. He is not here right now. But we want to move them way out of prescriptive antibiotics so we should want to encourage them initially to do over-the-counter but what we did in the health care law for flexible spending accounts was

disincentivize people using over-the-counter. In fact, we took away their ability to use their flexible spending accounts to do that. So I end up walking away having more questions than answers. And some of the questions I kind of already mentioned based upon the statements.

Does anyone want to—I guess let me just finish with a question with Dr. Spellberg, if I may. In your testimony you comment—we talked about this pipeline and development. Do you buy—I mean, you sat in here, and Dr. Woodcock left, and she was here for most of the testimony, which I have great respect for. Do you buy their arguments that they are doing all they can and there is a little uptick? You heard me ask them about regulatory authority, do they need more. I really didn't get any answer. So they seem to think they have the power to move forward but I have got a feeling that you are not convinced.

Dr. SPELLBERG. Well, let me start by saying that I think all of us are very appreciative of the tremendous energy and effort that Dr. Cox, Dr. Woodcock and the new leadership under Drs. Hamburg and Sharfstein have infused into the agency. Just in the last year or two we have seen a tremendous uptick of energy and efficiency and work product output. We have been asking for guidance documents for years on these diseases and we are finally starting to get some. I don't think that they need more statutory authority. I think that—there are two issues that I would raise with Dr. Woodcock's testimony. First is that it is not true that companies have a clear path to approval for superiority drugs. I consult for companies that develop antibiotics. They don't know how to do those studies. Those studies have never been done before. It may be philosophically true that that is an open path but for something that has never been done before, companies are not going to take a risk on hundreds of millions of dollars of capital invested to do a trial that has never been done before. They wanted to go to tried-and-truth pathways. So we think that we need guidance documents to do those studies. The superiority studies for highly drug-resistant bacteria do not exist. There is no pathway for that, and we need guidance on that, one.

Two, I think the issue with the non-inferiority studies that Dr. Woodcock mentioned, I don't think that there is—I would not personally characterize it as scientific controversy. What there is, is statistical controversy. If you talk to the physicians and the investigators who do these studies, there is pretty clear consensus on what these studies should look like, and when you look at the advisory committee panel votes, it is split, clinicians, scientists and statisticians. So I would personally go back to Samuel Clemens: There are three kinds of lies: lies, damn lies and statistics, and I think statistics are very valuable, but when you start to weigh them more heavily than clinical reality, I think that is a problem and I would like to see a philosophical balance. I think this is a philosophical problem, not a scientific problem at the FDA.

Mr. SHIMKUS. Thank you, Mr. Chairman. I want to apologize to the rest of the panelists for not asking follow-up questions but you can tell I was listening and I took in a lot of information. I yield back, Mr. Chairman.

Mr. PALLONE. Sure.

Next is, he has been characterized as our star, the gentleman from Utah, Mr. Matheson.

Mr. MATHESON. Well, thank you, Mr. Chairman. I have been called a lot worse, so I will take the positive descriptions when I get them.

I want to thank the panel. I am sorry I have been bouncing between two hearings, so trying to be in two places at once, but I do appreciate the panel being here. I appreciate your insight and your indicated support for what we are trying to do with the STAR Act, and Mr. Shimkus, I agree, there is always room to look for improvements and I have always tried to be an honest broker, and that is why we hold these hearings, to get more information and we want to do the best we can. Sometimes process does help if you go through the process, and so I hope we can continue to do that on this issue.

And I wanted to acknowledge Dr. Spellberg. You participated in a briefing just last month for Congressional staff that I think helped highlight this issue and it is good to see you again, and I appreciate your engagement on the issue, and both Dr. Spellberg and Dr. Bradley, I appreciate you bringing some examples of how infectious disease and disease-resistant bugs that cause the problems for actual patients because ultimately that is what we are talking about, the patients. And I have a bias because my wife is a pediatric infectious disease doc as well at the Children's Hospital in Salt Lake City, so this is an important issue for me and that is why I have tried to get engaged in this legislation.

Dr. Spellberg, let me ask you just a couple of questions. How often are seeing in your practice are you finding patients with resistant infections, and are you seeing a trend that is going in an upward way?

Dr. SPELLBERG. Yes. I am in an academic hospital so my patient care is inpatient, and we encounter multidrug-resistant bacteria daily, every day on rounds, and I will just give you an example. Over a 1-month period at my institution, we had 23 patients that were infected with extreme drug-resistant acinetobacter that is resistant to everything except one last-ditch drug, Colistin, which was abandoned in the 1960s because it is so toxic and that is all we have left. Twenty-three patients in one month for one bacteria. That is the scope of the problem.

Mr. MATHESON. And that was your last hope, that one medication?

Dr. SPELLBERG. Yes, that is it. And I should also mention, we don't routinely test for susceptibility to that drug so we don't know, some of those 23 patients may have been resistant to it as well. We don't know. Getting back to the STAR Act, we need data collection to know what the extent of the resistance problem is.

Mr. MATHESON. Right. Part of the STAR Act is, it does create this, we call it the public health antimicrobial advisory board, and it is going to include infectious disease experts, public health, pharmacy, vets and other experts to provide sort of advice to this inter-agency task force to try to bring some accountability to federal efforts. Do you think that—how do you think that type of advisory board is going to benefit this issue?

Dr. SPELLBERG. I think there are at least two really important reasons why we need that advisory board. One is that this stuff is very complex and it takes a tremendous amount of very broad scientific expertise. I think it is unrealistic to expect that one government agency is going to have that breadth of expertise. An external advisory panel can bring a very broad and deep expertise to oversee the issue. The second issue is that an external board can help hold the feet to the fire, help make sure that goals are met and provide some accountability externally.

Mr. MATHESON. In your practice, when you—well, you say you are at an academic hospital, teaching hospital, so in terms of your involvement with looking for development of new meds, new antibiotics that can address these tougher bugs, we had a lot of discussion today about the available incentives to encourage the research and development. Do you think the existing incentives, there are some that are working and not working in addition to what we ought to add in the future but are there some efforts we try to do to encourage development of new meds that just aren't getting traction at all?

Dr. SPELLBERG. Yes, I don't think we have any existing mechanisms that apply to antibiotics. We have tried to access the orphan drug program. It has been made very clear, explicitly clear that the orphan drug program does not apply to antibiotics for whatever reason. We need orphan-drug-like mechanisms. There is no existing incentive mechanism to bring companies back to the drawing board.

Mr. MATHESON. Mr. Chairman, I will yield back. Thanks.

Mr. SHIMKUS. Will the gentleman just yield for follow-up on that?

Mr. MATHESON. Yes.

Mr. SHIMKUS. In the orphan drug and because of the population of 200,000, is that basically why the FDA is saying that the orphan drug does not qualify? And since these are bacteria, they don't know the population?

Dr. SPELLBERG. You know, I think we could very much quibble with the fact that there are, you know—

Mr. SHIMKUS. Is this statistical stuff that you were talking about on my question?

Dr. SPELLBERG. I don't understand the exact reasons why the FDA counts the numbers as being more than 200,000. If we talk about all bacterial infections, certainly it is more than 200,000. If we talk about extremely drug-resistant acinetobacter, it can't be more than 200,000. But either way, fine. If we can't access orphan drug, let us look at other push-pull mechanisms and let us look at, you know, increasing funding at NIH so we can get better science to lead target discovery and establish a clinical trials network. There are lots of other things we could be doing.

Mr. MATHESON. Thanks, Mr. Chairman.

Mr. PALLONE. Thank you.

Dr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman. I can't tell you how refreshing it is to have a panel where four of the five panelists are MDs. You know, we did the health care bill and all the hearings leading up to that. We just heard from economists and political scientists and theoretical folks. It would have been great to have you

guys here while we were actually doing that work, but you are here today and I appreciate the fact that you are.

Dr. Bradley, Dr. Spellberg, you guys took me back to the 1970s when I was in medical school, and on the pediatric wards, the pediatric attending told us that let us use gandamycin because we are saving gentamicin for the days when gandamycin will no longer be effective. And then Dr. Spellberg, when I did an elective in infectious disease, I was told by the professor why did you pick gandamycin for this child. I said well, because we are saving gentamicin. He said well, you need to go down and talk to the orthopedist because they are not saving it, they are using it on anybody who walks in the door, which just—that is part of the problem because it is like our air quality issues. They don't live in a single jurisdiction, they tend to migrate throughout society.

But the 10 by 20 issue, Dr. Spellberg, you heard me questioning Dr. Woodcock from the FDA, and the new molecular entities in the last decade have been about 10, so is 10 by 20, are we just talking about the status quo with development of new stuff or is 10 by 20 really a breakthrough?

Dr. SPELLBERG. You are talking about 10 new molecular entities on a declining scale, so if you look at the last 5 years, it is way less than that. If we got 10 new meaningful drugs to treat really resistant bacteria by the year 2020, that would be a dramatic improvement from where we are right now. Do I think one drug per year is enough in the long term? Probably not. But if each of those drugs is a meaningful advance, it is not a “me too” drug, then one to two per year in the long run is probably enough to get us where we need to go.

Mr. BURGESS. Let me interrupt you because, again, they are just the devil on me with the gavel in this committee. What are some of the new things that are out there? What have you got in the pipeline? Tease us with what is over the horizon. What are we going to be able to treat?

Dr. SPELLBERG. To be honest with you, first of all, let us remember that if we are lucky, one in five drugs, one in five antibiotics in the pipeline is going to get approved. When you talk about the pipeline, you are talking about late pre-clinical early phase I clinical trials. It may be as bad as one in 10. So if you have 15 antibiotics in the pipeline, which is what the IDSA and the European Centers for Disease Control and EMEA identified, we are going to be lucky to have two, maybe three of those drugs get approved in the next 5 to 10 years or so.

Mr. BURGESS. Well, you talked quite passionately and eloquently about the need for funding, and I don't disagree with that, but 15 months ago we passed an enormous bill, it was called a stimulus bill. We pumped so much money into NIH, we thought they were going to pop, and now how do you get those discoveries into the hands of clinicians if we have got this pipeline problem at the FDA?

Dr. SPELLBERG. Well, I think you have got two problems there. One is putting money into NIH, and we are calling for \$500 million to go into NIAID specifically, is not enough. We need that money to go to the critical areas, and in our analysis with NIAID's help, the vast majority of the dollars they spent on antimicrobial resist-

ance is not spent on solving multidrug-resistant bacteria, it is primarily spent on things like HIV and tuberculosis. We need to have that money go to lead compound, discovery of new lead molecules that are going to treat multiresistant infections. A tiny fraction of that money goes there.

The other thing is, in discussions with Dr. Woodcock, we need a clinical-trial network so that very sophisticated clinical trials can get done that will open up the antibiotic pipeline during clinical development and we would like to see public-private partnerships, large grants that bring together academia and industry to help solve these problems.

Mr. BURGESS. Well, after all, that was the penicillin story because—

Dr. SPELLBERG. That is exactly right.

Mr. BURGESS [continuing]. Your 1942 pictures, however dramatic they are, that was only a handful of patients who could be treated at that time and it was not until the defermentation process occurred toward the end of the Second World War that it became clinically efficacious to treat large numbers of people and that was the story of D-Day, saving life and limb when they stormed the beaches of Normandy.

Dr. Fryhofer, I just have to ask you a question about the health care bill, because, after all, your organization supported it. I am a member of the AMA. I did not support it. I voted it against it. But on the issue of class II medical devices, and we are going to get—you are going to get hit, your members are going to get hit with a significant tax on class II medical devices in physician offices. Syringes, needles will be taxed and I think it is 2.9 percent. That is going to be a hard cost to pass on to the patient, to the consumer because you are under contractual arrangement with the insurance companies and it is not likely that they are going to pick up the cost of that tax. But what about some of these point-of-diagnosis tests that have been talked about, the tests are being developed by BARDA and some of the tests that Dr. Woodcock from the FDA talked about? Those tests, are they not going to be classified as class II and class II devices?

Mr. PALLONE. Dr. Burgess, why don't we do this? Your time has run out but the three of us, since we are here, I am going to have each of us have another 5 minutes.

Mr. BURGESS. We ought to let Dr. Fryhofer answer the question.

Mr. PALLONE. Answer that one and then—

Mr. BURGESS. Since it has been so eloquently posed.

Mr. PALLONE. Then we are going to have another round just for those—

Mr. BURGESS. Is this tax going to have a chilling effect on you being able to do those tests?

Dr. FRYHOFER. Well, I think that the tests that you are talking about would not necessarily be done in doctors' offices. I think many of these diagnostic tests would probably be done by a laboratory.

Mr. BURGESS. Well, if I can interrupt for a minute, that is exactly what we were told, that these would be point-of-diagnosis tests that would be done. The rapid strep was alluded to, and I

tried to get some information on some of the others but they will be done in the office.

Dr. FRYHOFER. Well, they may be collected in the office, but in order to be done in the office, you have to be CLIA approved to perform that level of test. So certainly I think some of these initial tests might not be performed in the office, and those are concerns and certainly as you say, there is a lot more work we need to do on this new health care bill but I think there are a lot of things we did accomplish. I have children, I have two college students, and I am glad to know that they can stay on my health insurance until they are 26. I am glad we have gotten rid of this preexisting-condition problem for so many of our patients. So there are some good things that happened but we still have a lot of work to be done and we are depending on you and Congress to work out the bugs and including these bugs we talked about today and move forward to help our patients.

Mr. PALLONE. Now you have another 5 minutes after, myself, Shimkus and you.

I wanted to ask a question of how we can promote the stewardship of antibiotics, encouraging more judicious use. In our first hearing on antibiotics, we heard about the CDC's Get Smart campaign, which is an effort to educate physicians and encourage better prescribing habits. We heard about some of the successes of that venture and some of the shortfalls in the funding for it. But even if Get Smart were fully funded, I am wondering if that goes far enough, especially if patients are demanding antibiotics. I am worried that a volunteer campaign won't be able to effectively address this issue or that even the interagency collaboration and what is proposed by Mr. Matheson under STAR might not be enough.

So let me just ask three questions in this regard, first of Dr. Bradley because I don't think we even asked you anything. As a pediatrician, can you talk about the pressures you face from parents to give antibiotics for your patients?

Dr. BRADLEY. Yes, sir. In the past that has been sort of standard. Both the parents ask for antibiotics for their children with sore throats, grandparents ask, and we have had a campaign with teaching materials in the waiting rooms, in the exam rooms to say don't ask for an antibiotic if your doctor doesn't think your child has an infection. There are programs we have put into place that have decreased antibiotic use, some of the CDC, some of them Academy of Pediatrics, and it is an education issue, and I think all of the press that—the lay press has a lot of information about antibiotic resistance. Parents are now understanding that we can't just give antibiotics out.

In another constructive way in different medical groups that are clinical pathways being developed where if a child has an ear infection, they come in with a supposed ear infection. There are specific ways that the doctor needs to evaluate that to make sure it is a true infection so there is the little checklist: is the eardrum red and bulging, is there pain, is there fever. And if not all of those are present, then there is no antibiotic that should be prescribed. We are putting together the same things for pneumonia so that we are designing methods for physicians and clinicians to assess children

in a systematic way to reduce inappropriate antibiotic use. So it is a huge problem and we are working hard and we are not there.

Mr. PALLONE. All right. I only have 2 minutes. I wanted to get into the hospital setting because I can see how these quality measures like Dr. Fryhofer, you mentioned better quality measures to track antibiotic use and I can see how that would work where someone has a cold or sinus and antibiotics shouldn't be used, but what about quality measures in the hospital setting? I will ask you, Dr. Fryhofer.

And then Dr. Spellberg, you laid out a comprehensive campaign for stewardship and you talked about comprehensive hospital programs. So let me start with you, same question. What do we do in the hospital setting? I will ask you and then Dr. Spellberg.

Dr. FRYHOFER. Well, certainly the hospital setting is a much different setting than the ambulatory setting. In the hospital, there is an opportunity for a very collaborative approach with the primary care or admitting physician, with infectious disease specialist colleagues, with clinical pharmacologists, also with the laboratory. So it is more of a real-time situation so you can sort of change your approach to the patient, you know, every hour, every minute, so to speak. In an ambulatory setting, right now we don't have as many quick diagnostic ways to know exactly what the patient has when they come in the office, and I think all of us were very impressed by the photo of that young woman that you showed us at the end of your presentation, Dr. Spellberg. But as a primary care physician seeing patients in my office every day, I don't want my patient to get like that. So we don't want every patient that gets an antibiotic to be on the verge of death. We want to use them judiciously. At the same time, we don't want to handcuff doctors because we are going to lose patients that way also.

Mr. PALLONE. Dr. Spellberg.

Dr. SPELLBERG. I have to answer your question in three parts but I will go quick. OK. So there are three strategies for stewardship. There is nagging, which I am going to make more comments about in a minute, and that is really important. There is diagnostics and there is approving drugs through the FDA in a completely new way, and all three of these things need to be done. In terms of the nagging, which is the traditional antibiotic stewardship program, I just want to point out what we are up against. If you go back to the historical literature which I spent a lot of time reading over the last several years, there were physicians in the 1940s that were begetting their colleagues not to overprescribe antibiotics. This is not a new conversation. It is very difficult to change human behavior. Stewardship programs have generally not been widely disseminated because there is no mechanism to pay for them. Hospitals won't pay people to spend their time nagging people not to prescribe drugs. So one of the issues is, we need the CDC to develop stewardship programs and that we need to figure out how to convince medical systems to pay for their implementation.

The second thing, probably the most powerful way we can prevent overuse of antibiotics is exactly what was just mentioned, look at the psychology of why antibiotics are overprescribed. It is fear, and I don't mean specific fear about lawsuits, I mean brain stem, we don't know why we are afraid fear because we don't know which

of our patients have bacterial infections or not. We have a patient with symptoms, it may be bacteria, it may be viruses. If 95 percent of the time it is viruses, it means 5 percent of the time it is bacteria, and I don't want to guess wrong. If we had rapid diagnostics, physicians have a printout that says this is not a bacterial infection, that will end inappropriate antibiotic prescription, so new diagnostics would be very powerful.

And the third thing is new FDA indications. If a drug is only indicated for the treatment of multidrug-resistant bacteria, it can only be marketed by law for what it is indicated for. That will prevent overuse of the drug in other settings.

Mr. PALLONE. OK. Thank you.

Mr. Shimkus.

Mr. SHIMKUS. Thank you, Mr. Chairman.

First of all, I have been told and I believe, although obviously you have heard me address some misgivings that FDA historically has been the gold standard and it has been able to help and roll out things. Obviously there are hiccups and there are problems now that we really want to address. There is also a concern in the pharmaceutical debate just in essence regular chemical compound drugs and maybe biologics that the new European Union and their pathway might eventually incentivize and have a quicker pathway which not only then moves new drugs and development over the European but then the factories and the jobs and then we lose that gold standard. Now we are talking about this continued problem here now with the antibiotic issue. You all are the experts and maybe Dr. Levi, maybe Dr. Spellberg, Dr. Bradley, some of whom are nodding as I look at facial expressions, does anyone want to weigh in? Is this European Union takeover, their ability to have a quicker pathway, one, is that a real threat? Two, is there stuff that we can learn in their processes which might help us move rapidly? Can anyone?

Dr. SPELLBERG. I will make a couple of comments and then I suggest that Dr. Eisenstein may be the most qualified to answer that.

Mr. SHIMKUS. Dr. Bradley wants to answer.

Dr. SPELLBERG. Oh, I am sorry. Go ahead.

Dr. BRADLEY. I can tell you that the way that the EMEA is approving antibiotics now includes strong programs for pediatrics upfront so after the first phase I trials where the drugs preliminarily tested in adults, they are not beginning to get testing in children so that they will have drugs for their children probably 5 years or so sooner than we would have them in the United States. Our FDA is talking to them, and I hope that we can get earlier programs in pediatrics, but yes, the EMEA and the Europeans have come at this with a completely fresh view and they are rattling cages and some of their ideas are quite good. Thank you.

Mr. SHIMKUS. Dr. Eisenstein.

Dr. EISENSTEIN. Yes. We get the impression, as Dr. Bradley just stated, that the EMEA is moving ahead in a more forward-looking way. I think that unfortunately the FDA had a hiccup with the approval process with Ketek. That has been very well documented. I won't go into details. But unfortunately, they, I believe, have gone into more of a risk-averse mode over the last 4 or 5 years, and one of my favorite expressions I learned from the director of infectious

diseases at the time, Janice Sheref, let us not have the perfect be the enemy of the good, and unfortunately, Janice is no longer at that position anymore, in part because of the fallout from Ketek and I think is very unfortunate.

Mr. SHIMKUS. Dr. Levi.

Mr. LEVI. I guess the two things that I would add is, one, I think we do have something to learn from how the Europeans are doing overall drug approval, but I also think that sometimes we are—you know, we need to recognize that the United States, for example, when we want the FDA process to move quickly, it can. We had the first approved H1N1 vaccines in the United States, even though our system is allegedly so much more cumbersome. So I think when we want to, we can make that system work.

The second is, we can't lose sight of the fact that it is not just—you know, the fact that there are so few new molecular entities entering the FDA stream is not because—it is not exclusively and probably not primarily because of the FDA approval process. We don't have the intellectual capital up front to create those, and we need to be investing in creating that intellectual capital and then maybe some of the financial capital will follow.

Mr. SHIMKUS. Let me just finish with this. I agree with you, Dr. Levi. The bioterrorism response that we did a couple Congresses ago and BARDA as an example of us when we realize that there is a real need to move, we can move. There are probably things to be learned in that process that would help us. I am concerned about the European Union and their ability to usurp us if we don't straighten out our processes to some extent, and this risk issue, the perfect is the enemy of the good is something that I think we just have to be careful about. I go back to the drug, the last drug, everything else is not of use. You go back to the drug developed in the 1960s that was super toxic but if I was a parent and that was the last hope, that also brings in liability issues. So there are processes, and I talked with Mr. Matheson. I think there are processes that members of good will can get some compromise on to move this forward, and I do appreciate the testimony today.

Mr. PALLONE. Thank you.

The gentleman from Texas, Mr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman.

Dr. Levi, you are right. We did get that vaccine, that H1N1 vaccine out in very, very short time, and the vaccine produced in this country turned out to be much safer than the vaccine produced in particularly some of the eastern European countries. So I will be the first to criticize the FDA, but I did want to point out that yes, they do sometimes do things right, and we do take safety in this country, we just stipulate that drugs are always going to be safe, but Dr. Eisenstein, you are right, we just clobbered them over Ketek. We had them in here every day for what seemed like weeks on end and it was a wonder that there was anyone left standing at the FDA. It wasn't this committee but the Oversight and Investigation Subcommittee that I am also on that was really pretty aggressive on that, not that there weren't problems but I think you are right, I think we as a subcommittee probably bear some of that responsibility because of the punishment we extracted on the folks on the FDA after that Ketek story broke.

Let me just ask you, Dr. Eisenstein, on the issue—I talked to Dr. Spellberg about this a little bit but the antibiotics in the pipeline concept. Do we have some good molecules in the pipeline that are going to be coming forward?

Dr. EISENSTEIN. I can speak mostly about Cubist. We are focused on acute health care. We have most of our expertise in the anti-infective space. We have now had daptomycin/Cubicin on the market for 7 years to specifically fight MRSA, and with that head of steam that we have established, we have three additional antimicrobials that are in human testing. One of them is for a disease called *Clostridium difficile* associated with diarrhea. You are a physician. You understand the importance of what. What others might not appreciate is that that is starting to come up on the horizon to become even as important perhaps as MRSA in the hospital setting. We are working on an antimicrobial specifically for that. We recently acquired a small company, an even smaller company than ours because we consider ourselves a madcap company looking at a new molecule to go after one of the six key escape pathogens, in this case *pseudomonas*, through a new mechanism of action that we are very excited about and we have yet another antibiotic also in the clinic that goes after some of the other escape pathogens including *pseudomonas*, *acinetobacter* and *Klebsiella*.

Let me underscore, though, something that Dr. Spellberg just said earlier, and that is, it is very difficult to be able to develop antimicrobials specifically for drug-resistant organisms because by definition, you don't have anything to compare it with so you therefore can't do a controlled clinical trial. This is exactly the comment made earlier about the statistics getting in the way of clinical judgment that makes otherwise great sense.

Mr. BURGESS. Let me just ask you a question on that. Some of the so-called market failures aren't really caused by a failure of science, they are caused more by the difficulties that we impose in the regulatory process?

Dr. EISENSTEIN. I would say that is part of it, and the other part is that then the market size later given the constraints that we have of putting some of these, I would say enormously potentially very valuable antibiotics. We talked some about personal interaction. I have a granddaughter who because of birth defects at birth, she is 3 years now, she has been through six urinary tract infections, three of which have been caused by these escape pathogens. I worry every moment that the next infection she is going to get is going to be due to an organism that is not going to allow her to live anymore. I mean, I am very personally invested in this. But the difficulty then is that we have the opportunity to come up with new antibiotics but then they have to be put behind a glass plate that says crack only in case of an emergency.

Mr. BURGESS. Yes, and I am going to interrupt you there because I am running out of time, and Dr. Spellberg, you referenced that and you said use only as indicated, but doctors, we use stuff off label all the time.

Dr. SPELLBERG. What we are talking about is a total rethink of how antibiotics are developed in this country and throughout the world. We can no longer afford the luxury of having a drug like tigecycline come out, which is a lifesaving drug for people with

really resistant acinetobacter and then have it get FDA approved to treat skin infections where we have 20 other antibiotics we can be using.

Mr. BURGESS. I just want to ask one last question on the advisory panel because this is a fight that the chairman and I had 3 years ago during the reauthorization of the Food and Drug Act, and you talked about philosophical flexibility in the advisory panels. We restricted the advisory panels such that anyone who had actually worked on development of a compound was restricted off of the panel, and this seemed to me to be awfully shortsighted. The Institute of Medicine in fact I think said restrictive to no more than 25 percent. But the way we went about that seemed awfully pernicious, particularly in some of the pediatric fields. The universe of people that has worked on the compound is—I mean, they are the people who know, the only people who know about the drug. So is what we have done with the advisory panels and the reauthorization 3 years ago, has that been part of the problem?

Dr. SPELLBERG. Well, I think the advisory panels have done the best they can overall. The real dissention recently has been a true clinician-statistician split, not an overall scientific split, although I do agree with you that I think the people who are the most experienced with clinical investigations are the people who tend to get consulted by companies. So if you exclude the most experienced, informed people, it does create problems, and Dr. Bradley has spent a lot of time in the advisory committee so I wonder if you want to make some comments.

Dr. BRADLEY. I thank you for your comment, sir, and I believe that keeping people off the committee who have any experience in developing the drugs has been a problem.

Mr. BURGESS. I thank both of you. I am glad the chairman was here to hear that. I will yield back my time.

Mr. PALLONE. Well, listen, this has been very helpful obviously and I think we learned a lot today, and again, we are doing three hearings in an ongoing effort and then we may move some legislation, so I really appreciate your input. We may give you additional written questions within the next 10 days or so and I would like you to get back to us promptly with that.

But thank you again, and without objection, the meeting of the subcommittee is adjourned.

[Whereupon, at 1:06 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

**Statement of Congressman Gene Green
House Energy and Commerce Committee
Subcommittee on Health
“Promoting the Development of Antibiotics and Ensuring Judicious Use in Humans”
June 9, 2010**

Mr. Chairman, thank you for holding this hearing on promoting the development of new antibiotics and ensuring appropriate use of antibiotics in humans.

Over the years individuals have become accustomed to receiving or even requesting a prescription for antibiotics when they see a doctor if they have a cold or other illness.

In many instances, antibiotics are not the appropriate course of treatment for a common cold. Antibiotics should only be used for bacterial infections, but because of their wide availability, they are often over-prescribed or over requested by patients.

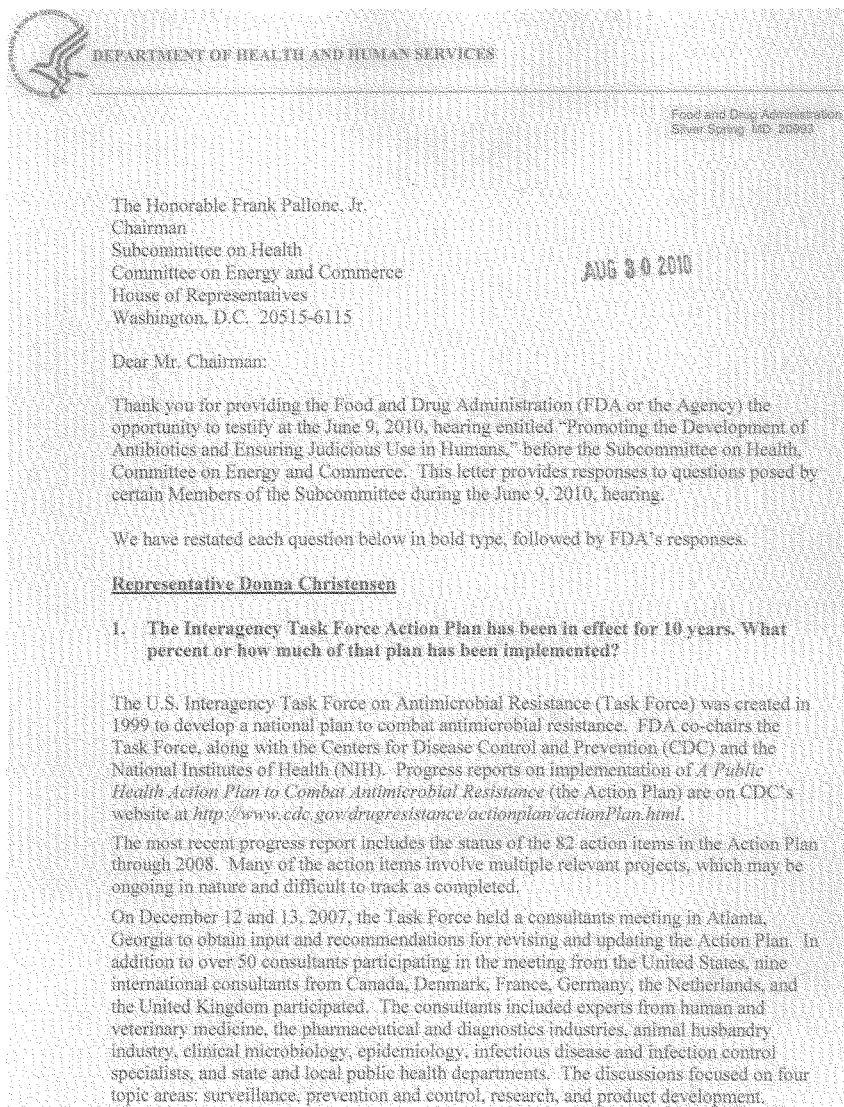
The overuse and misuse of antibiotics has led to increasing levels of antibiotic resistance, which as we know from a hearing we had a few weeks ago, the spread of these new antibiotic-resistant infections has serious public health consequences for our citizens.

Antibiotic-resistant bacteria may keep people sicker and for longer time, sometimes rendering them unable to recover at all. Our children, elderly, and those with weakened immune systems are especially vulnerable.

I also hope that we can invest in research and encourage the production and development of new anti-infective drugs.

Pharmaceutical companies are often hesitant to invest in the development of new antibiotics because the return on their investment is very small. In hearing the testimony today, I would like to see if we can encourage these companies to invest in the development of these medications.

Thank you again, Mr. Chairman, for holding this hearing and I look forward from hearing from our witnesses today on measures we can take to ensure and encourage appropriate use and prescription of antibiotics.



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The consultants reviewed the 2001 Action Plan in detail and made a series of recommendations for the Task Force to consider. Each recommendation is being reviewed and discussed by the Task Force, which in turn will revise the Action Plan with input from each of the federal agencies that comprise the Task Force. The revised Action Plan is currently being finalized by the Task Force and will be available for public comment in 2010.

Representative Ed Whitfield

1. What is the dollar value of the grants that would be available under the Orphan Drug program?

The Orphan Products Grant Program provides funding for clinical research in rare diseases. In terms of dollar values, grants are made up to \$400,000 per year in total costs for up to four years for Phase 2 and 3 clinical trials, and up to \$200,000 for up to three years for Phase 1 clinical trials.

2. What were the results of the April 28, 2008, public meeting on orphan antibiotic drugs and what are you doing to follow up on those recommendations?

FDA conducted a public hearing on April 28, 2008, in accordance with Section 1112 of the Food and Drug Administration Amendments Act (FDAAA). Section 1112 of FDAAA required FDA to “convene a public meeting regarding which serious and life-threatening infectious diseases, such as diseases due to gram-negative bacteria and other diseases due to antibiotic-resistant bacteria, potentially qualify for available grants and contracts under section 5(a) of the Orphan Drug Act (21 *United States Code* (U.S.C.) 360ee(a)) or other incentives for development.”

Speakers included physicians from the academic community, representatives from the Infectious Disease Society of America (IDSA), the Association for Professionals in Infection Control and Epidemiology, the Union of Concerned Scientists, the Clinical and Laboratory Standards Institute, the National Organization for Rare Disorders, and industry.

The hearing provided the infectious disease community, sponsors, and other interested parties an opportunity to discuss their experience with and concerns about the emerging threat of antimicrobial resistance, possible strategies fostering prudent use to prevent the development of antimicrobial resistance, and the potential for the provisions of the Orphan Drug Act or other incentives to facilitate antimicrobial drug development.

Although there was general agreement that incentives are needed for antimicrobial drug development, there was no consensus that the Orphan Drug Act would provide an effective incentive.

The *Federal Register* notice announcing the hearing can be found at <http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480508bf>.

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The transcript of the hearing can be found at
<http://www.regulations.gov/search/Regs/home.html#documentDetail?R=090000648054596>

FDA will continue to work with federal, state, local, and foreign government officials, medical professionals, the regulated industry, and all of FDA's stakeholders in developing sound strategies to facilitate antimicrobial drug development.

Representative Gene Green

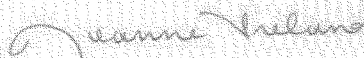
1. One of the suggestions for creating incentives for antibiotics is to expand the concept of tropical disease for already reviewed vouchers established under the FDA Amendments Act. Such a voucher would entitle the holder to get a drug reviewed with a target completion time of six months. Under such an approach, FDA would give a company a priority review voucher as a reward for developing a qualified infectious disease product. Could you tell us how the existing tropical disease program has worked for the FDA from the FDA's perspective? Does it seem like a workable approach for new antibiotics, and what are the trade-offs in terms of the FDA review of other drugs, if we had that six-month provision in there.

Since Congress enacted the priority review voucher (PRV) program, one voucher has been issued to Novartis for its anti-malarial product, Coartem. It is too early to assess the impact of PRVs on neglected diseases and global health; however, FDA is committed to making this program work.

If the Agency were to expand that incentive to include the development of new antibiotics, it is likely that the number of priority review vouchers issued would increase substantially. It is not entirely clear how such an expansion of this program would affect FDA review of other drugs, but it does raise some concerns, particularly with respect to the resources required to conduct reviews of new medical products. FDA generally allocates these resources by prioritizing, based on the potential impact on public health. If FDA were to grant a significant number of priority review vouchers, which ended up being applied to applications that would not ordinarily merit a priority designation, there could be a negative impact on our ability to review truly innovative products or address other priority public health issues in a timely manner.

Thank you for your interest in this matter. If you have further questions, please let us know.

Sincerely,



Jeanne Ireland
 Assistant Commissioner
 for Legislation