EXAMINING THE U.S. PUBLIC HEALTH RESPONSE TO SEASONAL INFLUENZA

HEARING

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED FOURTEENTH CONGRESS

FIRST SESSION

FEBRUARY 3, 2015

Serial No. 114–6

Printed for the use of the Committee on Energy and Commerce
energycommerce.house.gov

U.S. GOVERNMENT PUBLISHING OFFICE

94–848 PDF WASHINGTON : 2015

For sale by the Superintendent of Documents, U.S. Government Publishing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512–1800; DC area (202) 512–1800
Fax: (202) 512–2104 Mail: Stop IDCC, Washington, DC 20402–0001

COMMITTEE ON ENERGY AND COMMERCE

FRED UPTON, Michigan
Chairman

JOE BARTON, Texas
Chairman Emeritus
ED WHITFIELD, Kentucky
JOHN SHIMKUS, Illinois
JOSEPH R. PITTS, Pennsylvania
GREG WALDEN, Oregon
TIM MURPHY, Pennsylvania
MICHAEL C. BURGESS, Texas
MARSHA BLACKBURN, Tennessee
Vice Chairman
STEVE SCALISE, Louisiana
ROBERT E. LATTA, Ohio
CATHY MCMORRIS RODGERS, Washington
GREGG HARPER, Mississippi
LEONARD LANCE, New Jersey
BRETT GUTHRIE, Kentucky
PETE OLSON, Texas
DAVID B. MCKINLEY, West Virginia
MIKE POMPEO, Kansas
ADAM KINZINGER, Illinois
H. MORGAN GRIFFITH, Virginia
GUS M. BILIRAKIS, Florida
BILL JOHNSON, Ohio
BILLY LONG, Missouri
RENEE L. ELLMERS, North Carolina
LARRY BUCSHON, Indiana
BILL FLORES, Texas
SUSAN W. BROOKS, Indiana
MARKWAYNE MULLIN, Oklahoma
RICHARD HUDSON, North Carolina
CHRIS COLLINS, New York
KEVIN CRAMER, North Dakota

FRANK PALLONE, JR., New Jersey
Ranking Member
BOBBY L. RUSH, Illinois
ANNA G. ESHOO, California
ELIOT L. ENGEL, New York
GENE GREEN, Texas
DIANA DEGETTE, Colorado
LOIS CAPPS, California
MICHAEL F. DOYLE, Pennsylvania
JANICE D. SCHAKOWSKY, Illinois
G.K. BUTTERFIELD, North Carolina
DORIS O. MATSUI, California
KATHY CASTOR, Florida
JOHN P. SARBANES, Maryland
JERRY MCNERNEY, California
PETER WELCH, Vermont
BEN RAY LUJAN, New Mexico
PAUL TONKO, New York
JOHN A. YARMUTH, Kentucky
YVETTE D. CLARKE, New York
DAVID LOEBSACK, Iowa
KURT SCHRADER, Oregon
JOSEPH P. KENNEDY, III, Massachusetts
TONY CÁRDENAS, California

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

TIM MURPHY, Pennsylvania
Chairman

DAVID B. MCKINLEY, West Virginia
Vice Chairman
MICHAEL C. BURGESS, Texas
MARSHA BLACKBURN, Tennessee
H. MORGAN GRIFFITH, Virginia
LARRY BUCSHON, Indiana
BILL FLORES, Texas
SUSAN W. BROOKS, Indiana
MARKWAYNE MULLIN, Oklahoma
RICHARD HUDSON, North Carolina
CHRIS COLLINS, New York
KEVIN CRAMER, North Dakota
JOE BARTON, Texas
FRED UPTON, Michigan *(ex officio)*

DIANA DEGETTE, Colorado
Ranking Member
JANICE D. SCHAKOWSKY, Illinois
KATHY CASTOR, Florida
PAUL TONKO, New York
JOHN A. YARMUTH, Kentucky
YVETTE D. CLARKE, New York
JOSEPH P. KENNEDY, III, Massachusetts
GENE GREEN, Texas
PETER WELCH, Vermont
FRANK PALLONE, JR., New Jersey *(ex officio)*

C O N T E N T S

WITNESSES

SUBMITTED MATERIAL

EXAMINING THE U.S. PUBLIC HEALTH RESPONSE TO SEASONAL INFLUENZA

TUESDAY, FEBRUARY 3, 2015

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

The subcommittee met, pursuant to call, at 10:02 a.m., in room 2123 of the Rayburn House Office Building, Hon. Tim Murphy (chairman of the subcommittee) presiding.

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

Also present: Representative Ellmers.

Staff present: Charlotte Baker, Deputy Communications Director; Sean Bonyun, Communications Director; Leighton Brown, Press Assistant; Noelle Clemente, Press Secretary; Brad Grantz, Policy Coordinator, Oversight and Investigations; Brittany Havens, Legislative Clerk; Charles Ingebretson, Chief Counsel, Oversight and Investigations; Emily Newman, Counsel, Oversight; Alan Slobodin, Deputy Chief Counsel, Oversight and Investigations; Peter Bodner, Democratic Counsel; Elizabeth Letter, Democratic Professional Staff Member; and Nick Richter, Democratic Staff Assistant.

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

Mr. MURPHY. Good morning. Today we convene the first meeting of this session of the Subcommittee on Oversight and Investigation of the 114th Congress. I welcome back Members who served here last session, particularly, my friend and colleague, Diana DeGette, the ranking member from Colorado, and the new members from the 114th Congress, which we hope, as we come up, you may introduce them today, and I will introduce ours on our side.

The subcommittee is here to examine a very serious U.S. public health response to seasonal influenza. America is experiencing a severe flu season with an unstable predominant strain that could result in one of the deadliest and costliest flu seasons in recent memory. An estimated 50,000 people will die. Over 200,000 will be hospitalized, and most of these will be senior citizens.

Last February, when public health officials needed to decide what strains would go into this year's seasonal flu vaccine, the FDA bet on the wrong predominant strain. Just a few weeks after

the FDA's decision, doubts were already beginning to creep in the scientific community about the FDA's decision. By September, the U.S. vaccine was such a poor match for the dominant strain of flu that the World Health Organization, with consultation from the CDC, revised the vaccine formula, but not for the United States. It was changed for the Southern Hemisphere nations. In other words, the American people were stuck with a vaccine that wasn't going to work for nearly 4 out of 5 people, and for nearly 9 out of 10 seniors. Despite a growing body of knowledge that the vaccine for the United States would not be effective, production went forward anyway for a number of reasons that we hope to discuss today.

With a mismatched strain, this year's vaccine is estimated to be only 23 percent effective. It is even lower for the elderly at 12 percent. While this season's vaccine has a lower-than-usual effectiveness, CDC is still recommending vaccinations for everyone 6 months or older. In addition to vaccination, CDC has also recommended that all high-risk patients should be treated with antiviral drugs as soon as possible when influenza is suspected.

So what are agencies doing to communicate with the public? Many are choosing not to vaccinate against the flu because they hear the vaccine doesn't work, so why bother. We are seeing a similar result with measles vaccinations but for very different reasons, and now we are paying the piper for more than 100 cases have been stricken with a disease of measles that had once been eradicated from our shores.

False rumors still exist that vaccines and a preservative for multi-dose vaccines, which once used a microscopic amount of mercury as a preservative to prevent bacteria growth, led to autism. There is no credible evidence to support that claim. In fact, mercury is not used as a preservative in the MMR vaccine, and in developing nations where vaccination rates have increased, autism rates have not changed. So in addition to understanding why this year's flu vaccine missed so badly, and what should be done to protect the public in future years, I hope we can use this platform to educate the public and advance vaccine development in the interest of public health.

Now on to the flu vaccine. We must know: Did the Federal Government do everything it could at the right time to respond to the challenge of this year's flu season? As I noted, the CDC knew in late September that there was a significant mismatch, as great as 50 percent, with the U.S. vaccine, however, the CDC did not issue a health advisory in response to this mismatch until more than 2 months later. Did the CDC make the right public health decision to delay the health advisory, especially on delaying a recommendation to treat high-risk patients with antivirals? Could vaccine manufacturers have developed a new vaccine for high-risk groups? The CDC and the FDA tell us that the significant change in the strain could not have been addressed any earlier than September 2014, way too late to make changes in the U.S. vaccine. However, one flu expert at the University of Utah School of Medicine has stated on the record that there was a pretty good indication that the drifted strain by April or May 2014, that probably would have led to a de-

cision to change at that time if strain selection decisions for manufacturing were made in May instead of February.

In hindsight, it was a bad decision, and thousands will die. Surely there are lessons to be learned here to do something different in the future, and we want to know how we can partner with these agencies to come up with some solutions.

In 2009, when there was a similar outbreak of the swine flu, Federal agencies declared a public health emergency and responded by producing a monovalent, or single strain, vaccine to protect the public in a very short time. In only 12 weeks, they had developed this new vaccine. Here, we must know, was a monovalent rescue vaccine targeting the drifted strain a possible response? Who made the decision to not go forward with a different vaccine? If not, was this partly because the FDA and other agencies lacked emergency authority to respond? Did they recognize the problem and ask for authority to respond quicker? If an astounding 50,000 deaths and 200,000-plus hospitalizations does not equal an emergency then what is? Shouldn't we be treating this problem with more urgency, and is there even a backup plan in the event a vaccine mismatch to a deadly strain exists?

HHS has set a goal for vaccines to vaccinate 70 percent of their population as part of the Healthy People 2020 initiatives, but overall vaccination rates in the U.S. have been around 45 to 46 percent in the last few years. CDC has not even met its target of 50 percent. Does the CDC have an effective strategy to increase vaccination rates, or is there a better strategy for reducing flu deaths than seeking further increases of vaccination rates in all subgroups?

So we are here today to challenge some of the policies and decisions, but in the spirit of us all working together to make improvements in the public health response to seasonal flu. I am encouraged by the potential of ongoing research and innovation. We appreciate the cooperation and attendance of these excellent witnesses from the CDC, the FDA, NIH, and BARDA. We need your input to help us decide how we change this system for the better. I welcome our witnesses today, and thank them for help in this inquiry.

[The prepared statement of Mr. Murphy follows:]

PREPARED STATEMENT OF HON. TIM MURPHY

Today we convene the first meeting of the Subcommittee on Oversight and Investigations in the 114th Congress. I welcome back members who served here last session, particularly my friend and colleague, Diana DeGette, the ranking member, and our new members for the 114th Congress.

The subcommittee is here to examine the U.S. public health response to seasonal influenza. America is experiencing a severe flu season with an unstable predominant strain that could result in one of the deadliest and costliest flu seasons in recent memory. An estimated 50,000 people will die. Over 200,000 will be hospitalized, most of these will be senior citizens.

Last February, when public health officials needed to decide what strains would go into this year's seasonal flu vaccine, the FDA bet on the wrong predominant strain. Just a few weeks after the FDA's decision, doubts already were already beginning to creep in the scientific community about the FDA's decision. By September, the US vaccine was such a poor match for the dominant strain of flu that the World Health Organization, with consultation from the CDC, revised the vaccine formula—But, not for the United States. It was changed for the Southern Hemisphere nations.

In other words, the American people were stuck with a vaccine that wasn't going to work for nearly 4 out of 5 people and nearly 9 out of 10 seniors. Despite a growing body of knowledge that the vaccine for the United States would not be effective, production went forward anyway for a number of reasons we will discuss today.

With a mismatched strain, this year's vaccine is estimated to be only 23 percent effective. It's even lower for the elderly (12 percent).

While this season's vaccine has lower-than-usual effectiveness, CDC is still recommending vaccination for everyone 6 months or older. In addition to vaccination, CDC has also recommended that all high-risk patients should be treated with antiviral drugs as soon as possible when influenza is suspected. What are agencies doing to communicate to the public?

Many are choosing not to vaccinate against the flu because they hear the vaccine doesn't work, so why bother. We're seeing a similar result with measles vaccinations but for very different reasons, and now we're paying the piper as more than 100 have been stricken with a disease of measles that had once been eradicated from our shores.

False rumors still exist that vaccines and a preservative for multi-dose vaccines, which once used a microscopic amount of mercury as a preservative to prevent bacteria growth, led to autism. There is no credible evidence to support that claim. In fact, mercury is not used as a preservative in the MMR vaccine, and in developing nations where vaccination rates have increased, autism rates have not changed.

So in addition to understanding why this year's flu vaccine missed so badly—and what should be done to protect the public in future years—I hope we can use this platform to educate the public and advance vaccine development in the interest of public health.

Now on the flu vaccine, we must know: Did the Federal Government do everything it could at the right time to respond to the challenge of this year's flu season?

As I noted, the CDC knew in late September that there was a significant mismatch—as great as 50 percent—with the U.S. vaccine. However, the CDC did not issue a health advisory in response to this mismatch until more than two months later. Did the CDC make the right public-health decision to delay the health advisory, especially on delaying a recommendation to treat high-risk patients with antivirals? Could vaccine manufacturers have developed a new vaccine for high risk groups?

The CDC and the FDA tell us that the significant change in the strain could not have been addressed any earlier than September 2014, way too late to make changes in the U.S. vaccine. However, one flu expert at the University of Utah School of Medicine has stated on the record that there was a pretty good indication about the drifted strain by April or May 2014, that "probably" would have led to a decision to change at that time if strain selection decisions for manufacturing were made in May instead of February. In hindsight it was a bad decision—and thousands will die. Surely there are lessons to be learned here to do something different in the future.

In 2009, when there was a similar outbreak of the swine flu, Federal agencies declared a public health emergency and responded by producing a monovalent—or single strain—vaccine to protect the public in a short time. In only 12 weeks they had developed this new vaccine. Here we must know—was a monovalent "rescue" vaccine targeting the drifted strain a possible response? Who made the decision not to go forward with a different vaccine?

If not, was this partly because the FDA and other agencies lacked emergency authority to respond? Did they recognize the problem and ask for authority to respond quicker?

If an astounding 50,000 deaths and 200,000-plus hospitalizations does not equal an emergency then what is? Shouldn't we be treating this problem with more urgency?

Is there even a backup plan in the event of a vaccine mismatch to a deadly strain?

HHS has set a goal for States to vaccinate 70 percent of their population as part of the Healthy People 2020 initiative, but overall vaccination rates in the U.S. have been around 45 to 46 percent the last few years. CDC has not even met its target of 50 percent vaccination. Does CDC have an effective strategy to increase vaccination rates? Or is there a better strategy for reducing flu deaths than seeking further increases of vaccination rates in all subgroups?

So we're meeting here today to challenge some aof the policies and decisions, but in the spirit of us all working together to make improvements in the public health response to seasonal flu. I am encouraged by the potential of ongoing research and innovation. We appreciate the cooperation and attendance of witnesses from CDC, FDA, NIH and BARDA. We need your input to help us decide how we change this system for the better.

I welcome our witnesses today and thank them for their help in this inquiry.

Mr. MURPHY. And I recognize the ranking member for 5 minutes.

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

Ms. DEGETTE. Thank you so much, Mr. Chairman. I am really happy that our first hearing of this new Congress is on an area of bipartisan concern and interest. And I want to join you in welcoming our new members on both sides of the aisle to this committee. This is a venerable committee that has a long history of bipartisan investigations, and I think it is going to be a really important year to continue this trend.

Flu preparedness and response is incredibly important, and this committee has a long history of hearings and investigations on this issue. What we need to do is come together in support of a strong public health infrastructure that prevents outbreaks, and responds quickly and appropriately when they occur.

These past several months have been a harsh reminder that infectious disease is all around us. Last October and November, this subcommittee convened hearings on the Ebola outbreak and the dire situation in West Africa. We saw and, frankly, continue to see, the deadly consequences of a breakdown in the public health infrastructure there. Fortunately, we are now seeing the lowest number of new Ebola cases since last June, largely because of international efforts both to build and operate effective Ebola treatment centers, and also education of local populations on Ebola prevention and control. But, you know, it is interesting because as much attention as we have given to Ebola in this country, far more people die every month from influenza than they do of Ebola, and this is a continuing problem.

This month, we are hearing about the measles outbreak, which was linked to Disneyland in California and has now spread to at least 14 States. Infectious disease experts at the CDC and the State health departments have mounted a fast and aggressive response to prevent this highly contagious disease from spreading.

And, Mr. Chairman, I know you have received a letter from me and Ranking Member Pallone and Ranking Member Green asking this committee to hold a targeted hearing on the measles outbreak and the urgent public health threat. I would like to make a copy of that letter part of the record, Mr. Chairman.

[The information is available at the conclusion of the hearing.]

And, while that letter is pending, I want to commend you, Dr. Fauci. I saw you on the news last night telling all of the families in America to get their measles vaccine, and I really appreciate that. I want to add from this podium, as the mother of two daughters, one of whom is immunocompromised: Vaccinate your children against measles. There is no reason not to, and there is every reason that they could be a threat to themselves and other children if they don't get that vaccine. So I just want to pile onto that. It is very, very important.

But on to the flu, which is the topic of this hearing, the predominant strain of flu is H3N2, which is resulting in increased hos-

pitalizations, particularly for vulnerable populations like seniors and young children. And the CDC announced several weeks ago that the flu vaccine has only 23 percent effectiveness. That is significantly lower than in recent years, and as the chairman mentioned, it is largely due to changes in the virus that have resulted in a mismatch between the strain of the virus used in vaccine production and the one actually circulating. But even with a 23 percent effectiveness, we still need to protect ourselves as much as we can. Dr. Frieden reminded us several weeks ago that even a vaccine with 23 percent effectiveness will still prevent millions of people from getting sick. And so, therefore, as the chairman said, people also need to get this vaccine. And it is not too late; flu season is still going on. We have to do everything we can to protect our vulnerable populations; young children, seniors, pregnant women, and others with compromised immune systems.

So I am looking forward to hearing from our wonderful witnesses today about what we can do to mitigate the effects of this flu season, and how doctors and hospitals are prepared to respond. I also want to look to the future. What can we do to inform our prevention and response efforts in future flu seasons? I want to hear about the research and technological developments in diagnostics, antiviral treatments, and vaccines.

In our last hearing on this topic in February 2013, we heard about FDA approval of quadrivalent vaccines and cell base technology. Today, I am hoping our witnesses can give us encouraging news about the development of a universal flu vaccine.

So regardless of the particular effectiveness rate in a given season, the flu vaccine remains the best tool that we have to protect as many people as possible, and we need to have ongoing work on that. This flu season reminds us that it is almost impossible to predict what the strain will be, but it underscores the importance of a strong public health infrastructure.

And so, Mr. Chairman, I just want to say I appreciate the witnesses coming today. I hope we can all work together to move the country toward better flu preparedness.

Mr. MURPHY. I thank the gentlelady. And now recognize the chairman of the full committee, Mr. Upton, for 5 minutes.

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

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

This is an important issue, that is for sure, and it has been an especially harsh flu season, and preliminary estimates show that this year's vaccine is only 23 percent effective in preventing folks from going to the doctor for treatment, even lower for high-risk groups, which is often the case I know.

Usually, the flu vaccine is about 50 to 60 percent effective, and I, like many folks back in Michigan and across the country, would like to see us do better in addressing this major public health threat.

Every year, between 5 and 20 percent of Americans get the flu. In a severe flu season like this one, there could be more than 50,000 deaths, over 200,000 hospitalizations, and more than $10

billion spent on direct medical costs. The flu is and should be a top priority for all of U.S. public health.

This year's vaccine, we know, is less effective because it is not a good match for the flu strain that has become dominant. The flu virus strain changed significantly during the 6 months after the strain selection decision for the U.S. was made. The World Health Organization, in September, recommended changing the flu vaccine for the Southern Hemisphere to use in their upcoming flu season that starts in April but by the time the change in virus was evident, it was too late to change the U.S. vaccine.

Now, it is worth pointing out that the CDC continues to recommend vaccinations in the U.S., even with a lower effectiveness, and that high-risk patients should be treated as soon as possible with all antiviral drugs.

When we learned that there was a shift in the virus, what options were available to respond to the mismatch in viruses? Was there a way to deploy a rescue vaccine targeting just the changed virus? Was there a way to improve the effectiveness of this year's vaccine by adding substances to boost the immune response? Those are some of the questions that we need to have answered as we proceed with this hearing.

And I appreciate the folks that are testifying today and yield to Dr. Burgess and then to Marsha Blackburn.

[The prepared statement of Mr. Upton follows:]

PREPARED STATEMENT OF HON. FRED UPTON

Thank you, Mr. Chairman, for convening this hearing on the U.S. public health response to seasonal influenza. We remain in the midst of a particularly harsh flu season and preliminary estimates show that this year's vaccine is only 23 percent effective in preventing folks from going to the doctor for treatment, even lower for high-risk groups. Usually, the flu vaccine is about 50–60 percent effective. I, like many folks back in Michigan and across the country, believe we can do better in addressing this major public healththreat.

Every year between 5 percent and 20 percent of Americans get the flu virus. In a severe flu season like this one, there could be up to 50,000 deaths, over 200,000 hospitalizations, and more than $10 billion spent on direct medical costs. The flu is, and should be, a top priority for U.S. public health.

We understand that the reason this year's vaccine has lower effectiveness is because it is no longer a good match for the flu strain that has become dominant. The flu virus strain changed significantly during the six months after the strain selection decision for the U.S. vaccine was made, and we have been told it was too late to change the vaccine for the U.S. As a result of the evidence of change in the virus, the World Health Organization in September 2014 recommended changing the flu vaccine for the Southern hemisphere to use in their upcoming flu season that starts in April. The CDC continues to recommend vaccination in the United States, even with the lower effectiveness, and that high-risk patients be treated as soon as possible with anti-viral drugs.

While it is difficult to know when or how seasonal flu viruses are likely to change, leading to a need to change the vaccine for that year, we have made significant improvements in the past 10 years and it seems like we should be able to do better. There were known weaknesses in the surveillance system. In 2011, the World Health Organization conference found that a key test used to check for flu virus changes was not very effective in detecting evidence of changes in the deadliest flu strain. Our understanding is that this same test is still used. What tests were used as an alternative to the inadequate test?

And when we learned that there was a shift in the virus, what other options were available to respond to the mismatch in viruses? Was there a way to deploy a rescue vaccine targeting just the changed virus? Was there a way to improve the effectiveness of this season's vaccine by adding substances that boost the immune response?

Improving our response to a severe flu season with a mismatched vaccine could mean saving thousands of lives. My concerns and questions do not diminish my admiration and support for the dedication of the U.S. public health agencies working on flu preparedness. It is because of their talent and hard work that I believe improvement is really possible. We can work together to make that happen. I am also eager to learn about the latest research and innovation, and how we can better support and leverage these advances to improve our response to seasonal influenza.

I welcome all our witnesses, and look forward to their testimony.

Mr. BURGESS. I thank the chairman for yielding. And, Mr. Chairman, thank you for holding the hearing today.

In fiscal year 2014, the estimated Federal investment in seasonal flu preparedness exceeded $850 million. The public-private partnership driving research and development has had successes, but we must do better.

First, communication between agencies and with the public must improve. If there is a mismatch in the vaccine, which became apparent in May or even as late as September, it is unacceptable that advisories were not issued until December. Second, there must be transparency and consistency in the regulatory pathways for innovation in vaccines. Experts have recognized the promise of adjuvanted flu vaccines for over a decade, yet not one is licensed in the United States, and no guidance has been issued. Third, greater emphasis must be placed on modernizing the development and manufacture of flu vaccines. I would add my acknowledgement to the ranking member of the subcommittee, I too at one time was promised a universal flu vaccine, I think in this committee at a hearing just like this. That was probably in 2004 or 2005. We are still waiting. We want to see it.

So I appreciate the opportunity to be able to speak on this. I look forward to hearing from our witnesses.

And I will yield the balance of the time to Mrs. Blackburn, Vice Chair of the full committee.

Mrs. BLACKBURN. Thank you, Mr. Chairman. And I want to continue our conversation about vaccinations. And, yes, we are talking about flu today, but there is another issue out there and Ms. DeGette mentioned this. Vaccine politics injected into 2016, measles outbreak infects politics and debate.

Now, this is far too serious an issue to be treated as a political football. People still die from measles. And the CDC Web site tells us it was eliminated from the U.S. in 2000, but yet we are seeing this outbreak. And I have to tell you, it is of tremendous concern to me as a mother and a grandmother. I am hearing so much about this from my constituents, and they want to know some answers, they want to know how you all are addressing this. And I will tell you, when I hear about counties in California that have lower immunization rates than the Sudan and Chad, this is something that is of concern to me.

I am a Rotarian. We have invested decades into eliminating and wiping out polio, and then to hear this about the U.S., I am concerned.

We know the measles outbreak started in California. It has affected over 100 people in 14 States, and that most of those people were not vaccinated. So we do want to veer off and ask you some questions in this realm today.

And I yield back.

Mr. MURPHY. The gentlelady yields back. I now recognize Mr. Pallone for 5 minutes.

Mr. PALLONE. Thank you, Mr. Chairman, and thanks for holding this hearing today.

I have to tell Ms. DeGette that this is actually the first time that I have been a member of the O&I Subcommittee, so I am very happy.

Ms. DEGETTE. And we are happy to have you, Mr. Pallone.

Mr. PALLONE. Thank you.

Mr. MURPHY. Welcome aboard. It is the best subcommittee in Congress.

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

Mr. PALLONE. Thank you. So this year, we are seeing a severe flu season. Across the country, hospitalization rates are higher, especially for seniors over age 65, and for young children, and public health experts predict these flu activity levels will continue and even increase in the next few weeks.

The Centers for Disease Control and Prevention continues to recommend that we all get the flu vaccine. Initial estimates show that this year's flu vaccine is 23 percent effective, meaning that 23 percent of those vaccinated for the flu will still have to visit a doctor because of the flu. But despite being less effective this year than the recent past, flu shots will still protect against and decrease the severity of flu-related illnesses. Moreover, flu shots don't only protect the vaccinated, they also protect those who have not been vaccinated from getting sick, and as members of Congress, I think we all have to play a role to ensure that message gets out and it is not too late to get your flu vaccine.

This hearing is also a good opportunity to talk about how we can improve vaccination rates. We took important steps in the ACA to provide coverage for preventative services like immunizations. Since the law went into effect, nearly 76 million Americans have received no-cost coverage for preventative services, and as millions more receive coverage through the ACA, we hope to see the vaccination rate improve so that we can realize the benefits of a better-protected population. However, we still must improve public awareness, and continue to improve access to these preventative services. This is especially of concern as we hear reports of the measles outbreak that began at Disneyland, and is now spreading throughout the country. Just yesterday, the President urged all parents to get their children vaccinated against measles, and I would certainly echo his comments.

Dr. Tom Frieden, who heads the CDC, is warning that the U.S. could see a large outbreak of measles. There are now over 100 cases in 14 States, and measles is extremely contagious, 90 percent of those exposed to the disease will be infected unless they have been vaccinated. According to Dr. Frieden, there has been growing evidence that more parents are not vaccinating their children against measles, and that these lower vaccination rates have led to the latest increase in measles cases. The CDC is further assuring families, and parents especially, that the measles vaccine is safe

and effective, and we were able to eliminate measles in the U.S. in 2000, largely because of a highly effective vaccination program. So it is important to reiterate that measles is a preventable disease for which there are safe, effective and available vaccines.

So I look forward to hearing from our public health officials today about how we can improve vaccination rates for the flu, but we also need to learn how we can improve vaccination rates for the future for other infectious diseases, including measles.

I know that Ms. DeGette mentioned that both herself and Mr. Green and myself sent a letter yesterday asking for a hearing with regard to the measles public health emergency, and I hope that we can actually see that occur. I think it would be very important. And I just want to thank everyone.

And I would now yield the balance of my time to Representative Castor.

Ms. CASTOR. Well, thank you for yielding the time, and good morning. Thank you, Mr. Chairman and Ranking Member DeGette, for holding this important hearing to better understand the flu and the flu vaccine.

Vaccines are incredibly valuable tools to protect and improve the health of all of our neighbors. And as we have seen with the recent and surprising measles outbreak, vaccines protect lives. According to reports, there have been 102 cases of measles reported across 14 States, and those who do not vaccinate their children are putting them at risk, and they are putting others at risk. Vaccines are safe and effective.

I want to give particular thanks to Dr. Schuchat from the Centers for Disease Control for traveling to the Tampa Bay area a few months back to raise awareness with another important vaccine, the anti-cancer vaccine of HPV. Thank you for meeting with our public health students, and anti-cancer advocates to explain. See, Florida had one of the lowest rates of HPV vaccines, and we can save lives and prevent cancer if people will understand the importance of the HPV vaccine. Your visit was a great boost to our efforts to prevent cancer through the HPV vaccine, so thank you again for the work you do to educate the public on vaccinations.

You know, we are so fortunate to live in America where we have studied and investigated and tested all of these vaccines to ensure that they are safe and effective. So thank you to all the panelists for all the work you do, and I look forward to your testimony.

I yield back.

Mr. MURPHY. Thank you.

I would now like to introduce the witnesses on the panel for today's hearing. First is Dr. Anne Schuchat. Did I pronounce that correctly? The director of the National Center for Immunization and Respiratory Diseases at the Center for Disease Control and Prevention. Dr. Karen Midthun is the director for the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration. Dr. Robin Robinson, the director of Biomedical Advanced Research and Development Authority, otherwise known as BARDA, within the Office of the Assistant Secretary for Preparedness and Response. And Dr. Anthony Fauci is the director of the National Institute of Allergy and Infectious Diseases at the Na-

tional Institutes of Health. I welcome you all here and we look forward to your testimony.

I will now swear in the witnesses.

You are aware that this committee is holding an investigative hearing, and when doing so, has the practice of taking testimony under oath. Do any of you have any objections to testifying under oath? Seeing no objections, the Chair then advises you that under the rules of the House and the rules of the committee, you are entitled to be advised by counsel. Do any of you desire to be advised by counsel during your testimony today? Everybody has said no. In that case, if you would please rise and raise your right hand, I will swear you in.

[Witnesses sworn.]

Mr. MURPHY. Thank you. You are now under oath, and subject to penalties set forth in Title XVIII, section 1001 of the United States Code. You may each now give a 5-minute summary of your written statement. Make sure you pull the microphone close to you, and watch that red light.

Dr. Schuchat, you can begin.

STATEMENTS OF ANNE SCHUCHAT, M.D., DIRECTOR, NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES, CENTERS FOR DISEASE CONTROL AND PREVENTION, DEPARTMENT OF HEALTH AND HUMAN SERVICES; KAREN MIDTHUN, M.D., DIRECTOR, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES; ROBIN A. ROBINSON, PH.D., DIRECTOR, BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY, OFFICE OF THE ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE, DEPARTMENT OF HEALTH AND HUMAN SERVICES; AND ANTHONY S. FAUCI, M.D., DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH

STATEMENT OF ANNE SCHUCHAT

Dr. SCHUCHAT. Good morning, Mr. Chairman, and members of committee. I am Dr. Anne Schuchat, Director of the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention.

Influenza virus is a formidable adversary. Influenza's propensity to change presents unique challenges. New flu vaccines must be developed each year based on the predictions of which viruses are likely to be most common during the next season. Vaccine development is complex and time-consuming, typically requiring vaccine candidates that grow well in eggs and provide immunity in humans. And while we tackle seasonal flu, we must conduct constant global surveillance and prepare for the emergence of dramatically changed or shifted influenza virus that could trigger the next pandemic.

Over the past decade, we have made significant improvements in our ability to detect, prevent, and respond to influenza, yet, despite our improvements, the current severe influenza season has been difficult. My colleagues and I represent agencies that work together

to respond to seasonal and pandemic flu. The NIH supports research on vaccines, diagnostic tools, and antiviral drugs for seasonal and pandemic influenza. The Food and Drug Administration regulates influenza vaccines, convening public health and influenza disease experts to recommend which influenza virus strains should be included in FDA-licensed vaccines.

The Biomedical Advanced Research and Development Authority, BARDA, supports advanced research, development, and procurement of innovative medical countermeasures to address manmade and emerging infectious diseases, including influenza pandemics. And at CDC, we support surveillance and diagnostic capacity to rapidly detect, prevent, and respond to annual influenza epidemics, and novel and pandemic influenza threats.

Our CDC systems provide the scientific basis for global vaccine virus selection for seasonal flu, vaccine as well as for pandemic vaccine stockpiling. We monitor for genetic changes in the flu virus, and identify how these changes affect disease transmission and severity. We build public awareness and provide our knowledge about prevention and early treatment, and support public sector delivery of routine and emergency immunizations.

The 2014/15 influenza season has proven a particularly bad season. The virus that is predominant, H3N2, is associated with more severe disease. The vaccine we are using is not well matched to circulating H3N2 strains. Antivirals can be important aids in some patients, but clinicians are underutilizing them.

How do we find ourselves with vaccine that isn't well matched to the circulating H3N2 viruses? When the 2014/15 flu vaccine strains were selected last February, the drifted virus we are seeing now was not yet detected. A small number of these drifted viruses were first detected in March 2014, and CDC continued to monitor them throughout the summer, looking for genetic patterns and geographic spread.

In September 2014, when we began promoting seasonal vaccination, about ½ of the H3N2 viruses circulating were like the vaccine component. When the influenza season took off at the end of November, only ⅓ of the H3N2 viruses CDC detected were like the vaccine component. Our early vaccine effectiveness estimate found people vaccinated had about 23 percent lower risk of influenza infection requiring a medical visit. While this is lower than we usually see, the vaccine is providing some protection.

Influenza viruses follow their own schedules, not ours. New strains can emerge at any time. Some appear and die out, and others persist and spread. Our actions are proportional to risks. We work year-round to detect and characterize viruses of concern that circulate globally, monitor their emergence and geographic spread, and develop viable vaccine candidates for drift viruses as they occur. When we detected relatively small numbers of the drifted H3N2 strain late last spring, CDC began preparing candidate vaccine virus strains.

As the Nation's public health agency, we are committed to provide the information people need to protect their patients' and families' health, and to be transparent in our assessments and the evidence base that supports our recommendations.

As a physician and a public health professional, I too wish we could guarantee better protection each year, yet, we have made significant advances on several fronts. Our surveillance network is characterizing more viruses with improved methods. Significantly more Americans get flu vaccine each year, and information on viruses, disease, and vaccination is released more rapidly.

In closing, this flu season has caused more suffering and serious disease than many previous years, and there will be more challenging seasons ahead, but collaboration across the agencies, and with our public and private partners, holds promise for the future, including progress toward development of universal influenza vaccines, since better, broader, and long-lasting protection could transform our approach to this challenging virus.

[The prepared statement of Dr. Schuchat follows:]

Testimony before the
Committee on Energy and Commerce
Subcommittee on Oversight and Investigations
United States House of Representatives

Examining the U.S. Public Health Response to Seasonal Influenza

Anne Schuchat, MD (RADM, USPHS)
Director, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention U.S. Department of Health and Human Services

CDC
SAFER · HEALTHIER · PEOPLE™

For Release upon Delivery
Tuesday, February 3, 2015
Expected at 10:00 a.m.

INTRODUCTION

Good morning Chairman Murphy, Ranking Member DeGette, and Members of the Subcommittee. I am Dr. Anne Schuchat, Director of the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention (CDC). Influenza continues to be a significant public health burden and has proven, time and again, to be a worthy adversary to our best science; especially in a season where a change in the virus has presented unusual challenges to our control efforts.

Influenza is a contagious respiratory illness caused by influenza viruses. Risk of hospitalization and death from influenza is greater among the elderly, children under two years, pregnant women and others with chronic medical conditions. Each year between five percent and 20 percent of Americans are sickened by the virus, hundreds of thousands of hospitalizations occur and direct medical costs for hospitalizations and outpatient visits from complications of influenza exceed $10 billion.[1] The influenza virus is continually changing, necessitating new formulations of vaccine to be prepared and produced each year, thus requiring people receive annual vaccination in order to be protected.

Predicting influenza season requires constant public health and clinical vigilance to get the best information as rapidly and accurately as possible. Continual laboratory-based surveillance is needed to identify newly circulating viruses. The predominant circulating flu virus this year is the H3N2 subtype of Influenza A. H3N2 viruses, tend to cause more severe illness, particularly among the elderly. Influenza vaccination is, by far, the best available tool to prevent influenza. Since 2010, in the United States annual influenza vaccine has been recommended for everyone six months of age and over.

[1] Molinari et al. 2007, http://www.ncbi.nlm.nih.gov/pubmed/17544181

My colleagues and I represent the Agencies that comprise the collaborative partnerships that are essential for responding to both seasonal and pandemic influenza. The National Institutes of Health (NIH) supports research on influenza to inform the design of new and improved influenza vaccines, diagnostic tools, and antiviral drugs applicable to both seasonal and pandemic influenza strains. The Food and Drug Administration (FDA) is responsible for regulating influenza vaccines, and in this role, brings together public health and influenza disease experts to recommend which influenza virus strains should be included in FDA-licensed vaccines. The Biomedical Advanced Research Development Authority (BARDA) is mandated to support advanced research and development and procurement of novel and innovative medical counter measures such as vaccines, therapeutics, antiviral and antimicrobial drugs, diagnostics, and medical devices to address the medical consequences of man-made and emerging infectious diseases such as pandemic influenza and Ebola for the Nation.

At CDC we have spent decades building the surveillance and diagnostic capacity to monitor seasonal flu and rapidly detect novel influenza strains. Our systems are used to provide the scientific basis for vaccine virus selection – both for each season's flu vaccine as well as for pandemic vaccine stockpiling. We diligently monitor for genetic changes in the flu virus, and identify how those genetic changes affect disease transmission and severity. Our team builds public awareness and provider knowledge about the importance of vaccination, other prevention measures, and early treatment for influenza infection. These critical communication tools and partner networks are put to the test each influenza season, and are also crucial in the event of pandemic emergency. We work with public health and governmental partners at a global, Federal, state, and local level to respond to annual influenza epidemics as well as emerging novel and pandemic influenza threats. Just a decade ago, in October 2004, problems at one of the two manufacturers producing the great majority of flu vaccine for the United States resulted in a sudden loss of half of the Nation's expected supply of seasonal vaccine. This experience exposed the

Nation's vulnerability in preparedness for seasonal influenza and a possible pandemic, and exposed communication and programmatic challenges related to vaccine distribution. Since then, collaborative efforts across the Federal Government and the private sector, have led to improved influenza vaccine technologies that have either expanded vaccine supply or improved vaccine effectiveness, and in some cases, accomplished both of these goals. Today seven different companies produce flu vaccine for the U.S. market, offering newer formulations such as live attenuated influenza vaccines, thimerosal preservative-free, high dose inactivated, intradermal, cell-based, recombinant, and quadrivalent products. A network of improved domestic and international surveillance and monitoring systems provides timely vaccine virus updates and vaccine coverage and effectiveness estimates; more treatment options exist than before; and progress is being made towards the development of a longer-lasting and more broadly protective universal flu vaccine.

CURRENT SEASON

Influenza activity often increases in October and can extend as late as May. While flu seasons are unpredictable in terms of their timing, peak, duration, and severity, they have lasted an average of 13 weeks each year of the past decade.

The current influenza season began the week of November 23, 2014, and flu quickly became widespread across most of the country. To date, this season has been severe, with hospitalizations among the elderly exceeding that observed in the past five years through this point in the season, and the vast majority of illness caused by influenza A H3N2. These patterns are characteristic of a flu season where the dominant circulating strain is H3N2.

STRAIN SELECTION

The flu viruses selected for inclusion in seasonal flu vaccines are updated each year based on data collected by 142 national influenza centers in 112 countries, conducting influenza surveillance. These laboratories send influenza viruses to one of the five World Health Organization (WHO) International Collaborating Centers for influenza; CDC's Influenza Division is one of these WHO collaborating centers. These data show us which influenza viruses are circulating, how they are spreading, and detect whether circulating viruses are drifted away from vaccine strains. They also help us generate surveillance-based forecasts about which viruses are most likely to cause illness during the coming season.

Twice each year, CDC and other global public health partners participating in the WHO network review data on thousands of influenza viruses to select four representative candidate vaccine viruses (1 influenza A H3N2 virus, 1 influenza A H1N1 virus, 1 influenza B Yamagata lineage virus, and 1 influenza B Victoria lineage virus). For the Northern Hemisphere, these viruses are selected in late February of each year. For the Southern Hemisphere, these viruses are selected in September. These decisions are made many months before the influenza season starts to provide time for vaccine manufacturers to prepare and harvest vaccine viruses and produce vaccines that can be released for use.

WHO recommends specific vaccine viruses for inclusion in influenza vaccines based on all of the surveillance information; however, each individual country must decide which vaccine candidate viruses should be included in influenza vaccines licensed in their country. . In the United States, the U.S. Food and Drug Administration (FDA) determines which vaccine viruses will be used in U.S.-licensed vaccines for the upcoming influenza season, taking into consideration recommendations made by the WHO and FDA's Vaccines and Related Biological Products Advisory Committee. It takes at least six months to produce large quantities of influenza vaccine. Because of these production schedules and the variable

timing and duration of influenza seasonal activity, the selection of vaccine viruses for the next season is often made in the middle of the current season. For example, the 2014-2015 season is ongoing, but decisions about the viruses to be included in the vaccine for the 2015-2016 season will be discussed at WHO later this February, followed by a meeting of the FDA's advisory committee, which makes recommendations for the FDA-licensed influenza vaccines. CDC and the WHO influenza surveillance network will continue throughout the year to collect and characterize new viruses as potential vaccine candidates.

DRIFTED VIRUSES

Antigenic drift happens when there are small changes in the genes of influenza viruses that gradually occur over time as the virus moves through the millions of people that are infected each year. These small genetic changes are inevitable and occur, in a sense, as a way for the virus to evade the protection afforded by past infection or vaccination. These genetic changes can occur at any time, and in any location around the globe. The 2014-2015 Northern Hemisphere vaccine viruses were selected in February 2014, and were based on strains that were circulating worldwide at that time. In the months following the annual virus selection, CDC's routine surveillance identified a small number of influenza H3N2 strains which had drifted and were not covered by the vaccine viruses chosen in February. The first of these drifted viruses was detected on March 8, 2014. Through the spring of 2014 (March through the end of May), drifted viruses represented only 17 percent of the hundreds of specimens collected and tested at CDC during that time.

Drift variants emerge and die out frequently. When a drifted virus first emerges, there is no way to predict if and when it will die out or circulate widely. Over the summer of 2014, the drifted H3N2

viruses were detected in greater proportions and became more common among H3N2 viruses in the United States and abroad. Forty-nine percent of the 47 H3N2 viruses collected worldwide in September 2014 and characterized by CDC were drifted from the H3N2 Northern Hemisphere influenza vaccine virus component. Based on CDC and other WHO Collaborating Center surveillance data, one representative virus of these drifted H3N2 viruses was selected in September 2014 for inclusion in the Southern Hemisphere vaccine. As of January 23, 2015, 64 percent of H3N2 viruses collected in the United States and characterized by CDC were drifted from the H3N2 vaccine virus component. Interim vaccine effectiveness estimates available at the beginning of January confirmed our concerns of reduced protection from this year's seasonal influenza vaccine. These mid-season CDC studies determined that receiving an influenza vaccine reduced a person's risk of going to the doctor for laboratory-confirmed influenza illness by about 23 percent, a level that was less than half the effectiveness of vaccines in years where the match was much better. While these mid-season estimates are preliminary, they help CDC and others tailor prevention and control messages and policies during the season, helping make the public health response more nimble and appropriate to the evolving situation.

While we sometimes see that antibodies made in response to vaccination with one flu virus can provide protection against different but related viruses, our early vaccine effectiveness estimates this season suggest that there is little cross-protection against the drifted H3N2 viruses. However, vaccinated people are still better protected than those not vaccinated—the vaccine is preventing some illness caused by H3N2, and because the flu vaccine protects against other influenza types (H1N1, B), people who got vaccinated are likely to be protected against other viruses that may circulate later in the season. For these reasons, CDC continues to recommend flu vaccination, however we have increased alerts about the importance of other approaches to mitigate the complications of the severe influenza season.

ANTIVIRAL MEDICATIONS

Antiviral drugs become even more important when circulating flu viruses vary from the vaccine viruses. Antivirals can reduce duration of illness by a day, improve patient outcomes in the hospital, and reduce spread, especially if given within 48 hours of illness onset. These are not perfect drugs and they have limitations, however they are the only drugs available for the specific treatment of influenza infection. Antiviral drugs are approved by the FDA for the treatment of uncomplicated influenza, based on data submitted during the licensure process from randomized controlled trials, which have generally targeted relatively healthy populations and outpatient illness. A large and growing body of data from various studies shows that these drugs can prevent more serious flu outcomes, such as pneumonia and hospitalizations. Among hospitalized patients, the risk of death was reduced when antiviral drugs were used. These drugs are especially important for populations at increased risk for complications from the flu, including young children, pregnant women, and the elderly.

We also know that these drugs are underused by physicians.[2] As soon as CDC determined that the vaccine might have less benefit than usual, CDC increased its communication efforts around the appropriate use of influenza antiviral drugs, by issuing health alerts and media updates, convening clinician networks, and disseminating messages and guidance through public health, clinician organization, and community-based partners. Antiviral drug manufacturers have stated they have sufficient product on hand to meet the projected high demand during the 2014-2015 influenza season.

PREPARING FOR THE NEXT PANDEMIC

Investments in strengthening control of seasonal influenza contribute to pandemic preparedness. The systems we have in place for seasonal influenza are a part of the same systems we use to prepare for and respond to an influenza pandemic. For example, CDC's robust surveillance network identified the

[2] http://www.cdc.gov/flu/news/influenza-prescribing-study.htm; http://cid.oxfordjournals.org/content/early/2014/07/09/cid.ciu422.abstract

emergence of the drifted H3N2 seasonal virus, but also aids in detection of novel, avian, and swine-origin influenza viruses causing disease in humans. CDC's increased surveillance has led to a greater number of viral specimens received, viruses of concern identified, and candidate viruses created for seasonal and pandemic vaccine manufacturing. Our systems allow us to detect new viruses; assess virus' transmissibility; provide information to enable vaccine production; promote treatment with antiviral drugs; and communicate with the public and medical community.

Improvements to our seasonal influenza response also serve to strengthen the effectiveness of our pandemic response. Pandemic influenza is a formidable security threat due to the potential for substantial excess illness and death as well as multisector disruption. Pandemics can emerge anywhere, and early detection of novel influenza is critical to an effective response. Robust networks of global partners are critical in helping to protect the Nation. CDC has 57 bilateral cooperative agreements with partner nations to enhance their capacity to detect and respond to influenza. Of note, this capacity-building effort is also benefiting other respiratory pathogen detection and prevention work. CDC provides technical assistance to help these countries collect data. These data provide an evidence base to adopt robust influenza vaccination policy and recommendations. We have seen an impact from supporting our global partners as evidenced by the increasing number of vaccine virus candidates from these countries, as well as the detection and response to avian influenza cases.

The wide distribution of CDC's diagnostic test kits to hundreds of partner laboratories around the globe helps to monitor seasonal influenza and provide vaccine viruses for use in annual vaccines. This capability also can detect novel avian and swine influenza viruses which occasionally cause illness in humans. CDC has designed its diagnostic tests to detect both seasonal and novel infections, leading to first detections of the newly emerging pandemic H1N1 in 2009, and more recent infections with swine

influenza viruses occurring in fair-goers in the U.S. Because of the ability to detect novel influenza virus infections, CDC is prepared to test for any possible human infection with the recently identified avian H5N8 and H5N2 influenza viruses that have been detected for the first time in the U.S. in the Pacific Northwest.

Progress over the Past Decade

Substantial improvements have occurred during this past decade. In 2005, in response to the emerging, highly pathogenic H5N1 influenza in Asia, the National Strategy for Pandemic Influenza was released; and one year later, the Pandemic and All-Hazards Preparedness Act (PAHPA) was signed into law. These set the standard for the US Government response to influenza preparedness and response. Response to the 2009 H1N1 influenza pandemic further strengthened the nation's capacity to detect and respond to influenza threats.

In 2004, CDC fully sequenced 241 virus specimens compared to 1,832 in 2014. In 2005, there were no FDA-approved PCR (**polymerase chain reaction)** kits to test for influenza; today, CDC has submitted and received FDA-approval for 11 different influenza diagnostic PCR test applications. State and local public health labs are capable of detecting novel influenza strains including H5 and H7N9 strains. As a result of the 2004 flu vaccine shortage, approximately 58 million doses of vaccines were available in the U.S. market that season; to date, more than 147 million doses of vaccine have been distributed in the United States this flu season. Over the past few years, through the combined efforts of USG agencies working closely with manufacturers, we now have 14 influenza vaccines produced by seven manufacturers. This is an increase from five seasonal influenza vaccines that were available in the US market in 2006.

In 2005, 19 percent of Americans were vaccinated against influenza; last season, the coverage rate was up to 46 percent. In the 2005-2006 flu season, we averted 1,300,309 cases of influenza through vaccination; last year's season saw 6,787,615 cases of flu averted.[3,4] Finally, CDC has expanded the number of countries supported through international cooperative agreements to build influenza surveillance capacity from nine in 2004, to 57 today.

The Future Fight Against Influenza

Rapid laboratory identification of influenza, such as advanced molecular detection (AMD) using next-generation molecular sequencing to reveal a virus' complete genetic information, make it easier to identify changes in an influenza virus' genome. This has improved the speed of our detection and response to new variants of influenza. Using AMD methods to obtain complete genetic data without growing cultures in the lab has reduced the time needed to detect emerging threats and reduce response times. These methods are being applied to enhance virus genetic data that informs influenza vaccine virus selection, vaccine development, risk assessment, and investigation of the source of the disease.

CDC participates in the Biomedical Advance Research and Development Authority (BARDA)-led initiatives to improve manufacturing of current vaccines and support development of better influenza vaccines. Part of this effort is the development of a "universal vaccine" that would offer better, broader, and longer-lasting protection against seasonal and novel influenza viruses. A number of government agencies and private companies have begun work to advance development of universal flu vaccines.

---

[3] Kostova D, Reed C, Finelli L, Cheng PY, Gargiullo PM, Shay DK, Singleton JA, Meltzer MI, Lu PJ, Bresee JS. Influenza Illness and Hospitalizations Averted by Influenza Vaccination in the United States, 2005-2011. PLoS One. 2013 Jun 19;8(6):e66312. Print 2013. PubMed PMID: 23840439; PubMed Central PMCID: PMC3686813.

[4] http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6349a2.htm

In support of U.S. universal influenza vaccine efforts, CDC used cutting edge genomic technologies to develop two candidate vaccine viruses for use in universal influenza vaccine human clinical trials sponsored by the National Institutes of Health (NIH). In July 2014, CDC sent these vaccine viruses to an Australian vaccine manufacturer contracted by BARDA to produce the clinical lots for vaccine trials. Phase 1 clinical trials to be conducted by NIH are scheduled to start in 2016.

CONCLUSION

Influenza viruses present us with unique challenges. Unlike other vaccine preventable diseases, influenza is constantly changing. The investments made by the U.S. government for the diagnosis, prevention, and control of influenza have led to increased domestic and global viral surveillance, an increase in knowledge about how the flu virus works, more choices of vaccine types, increases in the number of cases averted due to vaccination, and expanded recommendations of influenza vaccination to all age groups (above the age of six months) and increased use of influenza vaccine among children and pregnant women.

Although many gains in seasonal and pandemic influenza preparedness and control have been made over the years, continued improvements are needed. We will work, along with our government, academic, and industry partners, to improve use of antiviral treatment, to make more effective influenza vaccines, and to speed production of existing vaccines for all Americans.

As we work together toward the goal of universal influenza vaccines, CDC will continue to work 24/7 to identify ways to improve methods of diagnosis, prevention, and control of influenza and respond to influenza threats here and around the world.

Mr. MURPHY. Thank you.

Dr. Midthun, you are recognized for 5 minutes. Thank you. Make sure the microphone is turned on and it is close to you. Thank you. You still have to turn it on. Press the—there you go.

STATEMENT OF KAREN MIDTHUN

Dr. MIDTHUN. Thank you. Mr. Chairman and members of the subcommittee, I am Dr. Karen Midthun, Director of the Center for Biologics Evaluation and Research, the center within FDA that is responsible for regulating vaccines. Thank you for the opportunity to be here today to discuss our role in a highly collaborative, multi-partnered effort in preventing influenza through vaccination in the U.S.

Influenza viruses continually undergo changes in their genetic makeup, and the resulting proteins that interact with the immune system. Due to these continuous changes, the composition of influenza vaccines must be periodically updated so that they are effective against what are anticipated to be the predominant circulating viruses in the upcoming influenza season.

The strains of virus in the vaccine include 2 distinct subtypes of influenza A, H1N1, and H3N2, and 1 or 2 influenza B strains, depending upon whether the vaccine is trivalent or quadrivalent. To identify virus strains likely to cause illness during the upcoming season, the World Health Organization convenes influenza and public health experts to study recently circulating influenza viruses from around the world, and recent global disease patterns. After careful evaluation of the assessment, WHO makes recommendations on the composition of the influenza vaccines, usually in late February for the upcoming season in the Northern Hemisphere, and in September for the upcoming season in the Southern Hemisphere. The recommendations must be made months in advance because of the time required for manufacturing, testing, lot release, and distribution of a very large number of vaccine doses.

Each year, following the WHO recommendations, FDA convenes its vaccines and related biological products advisory committee, typically in late February or early March. The committee considers the WHO recommendations and reviews information regarding viruses that caused illness in the previous year, how these viruses are changing, and disease trends. Based on the data available at the time of the meeting, the committee makes recommendation for the composition of the influenza vaccines licensed by FDA for the upcoming season in the U.S. Once the strains are selected, candidate influenza viruses that are adapted for high growth are generated and accepted by WHO collaborating centers, and are provided to manufacturers who generate the seed viruses for manufacturing vaccines. The manufacturing demands are tremendous and the timelines are tight. No other vaccine is produced, FDA approved and distributed every year across the U.S. within a six-month time frame.

This season, more than 150 million doses were manufactured. Given the yearly need for a new vaccine, there is limited flexibility in the timelines of vaccine manufacturing and availability. And parallel with vaccine manufacturing, FDA develops and calibrates reagents which are used by both FDA and the manufacturers to

test vaccines for potency and identity before FDA approves the new formulation for distribution. Manufacturers submit their vaccine testing results, along with samples from each lot, to FDA for lot release. As FDA releases lots, the manufacturers can make these lots commercially available throughout the U.S.

In February 2014, when the strain selection recommendation for the current influenza season was made, it reflected the circulating viruses. The drifted H3N2 viruses were first detected in March 2014 and were uncommon. Over the ensuing months, the drifted strains gradually increased. By late September, when WHO made its recommendations for the 2015 Southern Hemisphere influenza vaccine, the drifted H3N2 strains were common, prompting a recommended change in the upcoming Southern Hemisphere vaccine composition. Because of the manufacturing time required, there was not enough time to make a similar change for the current Northern Hemisphere influenza season. The drifted strains have caused the majority of influenza cases this season, however, vaccination is still important to prevent disease and minimize the public health burden of influenza. Influenza vaccines contain three or four influenza viruses, so even when there is a less than ideal match or lower effectiveness against one virus, the vaccine may protect against the other viruses.

FDA has made progress in our preparedness efforts and collaboration with BARDA, CDC, NIH, manufacturers, and other stakeholders, and we thank Congress for your support of these efforts. New influenza vaccines have been licensed, including cell-based, recombinant protein vaccines and quadrivalent vaccines. To enhance pandemic preparedness, FDA licensed an adjuvanted H5N1 avian influenza vaccine, and has worked with U.S. Government partners and manufacturers to facilitate the development of candidate vaccines directed at H7N9 avian influenza. Surveillance efforts are more extensive than ever before, and offer the potential for early detection of emerging viruses. The number of candidate vaccine virus strains available to manufacturers has greatly increased over the last few years, providing them with more options to increase vaccine yields. We continue efforts with our Government partners to develop high-yield candidate vaccine strains, as well as more modern, faster testing methods for vaccine potency and sterility. To further address the challenges presented by the constantly changing nature of influenza viruses, scientists and Government laboratories, academic institutions, vaccine manufacturers, are all working to develop new generation vaccines that might provide longer-lasting and broader protection against influenza viruses, including drifted strains. Although these development efforts are still in early stages, some may have the potential to increase and broaden protection against influenza.

FDA will continue to work with its Government partners, manufacturers, and other stakeholders to facilitate development of new vaccines, and identify methods that have the potential to speed the manufacturing process for existing vaccines. Our goal is to better protect the American public against influenza.

Thank you.

[The prepared statement of Dr. Midthun follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT

OF

KAREN MIDTHUN, M.D.

DIRECTOR, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

"FDA's Role in Preventing Influenza and Protecting the American Public Through Vaccination"

BEFORE THE

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

February 3, 2015

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Karen Midthun, Director of the Center for Biologics Evaluation and Research (CBER), which is the Center in the Food and Drug Administration (FDA or the Agency) responsible for regulating vaccines. Thank you for the opportunity to be here today to discuss FDA's role in the highly collaborative, multi-partnered effort in preventing influenza through vaccination in the United States.

Influenza is a major public health concern that annually causes illness in a substantial proportion of the U.S. population and may result in serious complications, including hospitalization and death. Influenza viruses are highly unpredictable, and each year can present new challenges for vaccine manufacturers, public health agencies, the medical community, and patients. Influenza viruses continually undergo changes in their genetic makeup and the resulting proteins that interact with the immune system. These changes can occur from one season to the next; they can also occur within the course of an influenza season. Minor changes in the protein structure in influenza viruses, known as "antigenic drift," occur frequently, enabling the virus to cause repetitive influenza outbreaks by evading immune recognition. These changes also have the potential to decrease the effectiveness of the vaccines targeting these protein structures. Major changes, known as "antigenic shift," can also occur and have the potential to lead to a pandemic, as we experienced in 2009. Unlike other vaccines, the composition of influenza vaccines must be periodically updated so that they are effective against what are anticipated to be the predominant circulating viruses in the upcoming influenza season. The strains of virus in the vaccine include two distinct subtypes of influenza A (H1N1 and H3N2) and one (for trivalent

vaccine) or two (for quadrivalent vaccine) different lineages of influenza B (B/Yamagata and B/Victoria, which are genetically divergent from each other).

Virus Strain Selection—A Worldwide Process to Ensure the Timely Availability of Influenza Vaccine

The process of ensuring the timely availability of influenza vaccine in the United States and elsewhere is a global, year-round process. Each year, the World Health Organization (WHO) convenes technical consultations in February and September to recommend the virus strains for inclusion in influenza vaccines for the Northern and Southern Hemispheres, respectively. FDA participates in both of these technical meetings. To identify virus strains likely to cause illness during the upcoming influenza season, influenza experts from the WHO's Collaborating Centers for Influenza—which includes the Centers for Disease Control and Prevention (CDC), the WHO Essential Regulatory Laboratories, which includes FDA's CBER, and other influenza and public health experts—study recently circulating influenza viruses from around the world and recent global disease patterns. In addition, blood samples from individuals receiving the most recent influenza vaccines are analyzed by the WHO Essential Regulatory Laboratories to determine how well antibodies induced by these vaccines react to recently isolated viruses. These Essential Regulatory Laboratories are located in national regulatory agencies and have a critical role at the global level for developing, regulating and standardizing influenza vaccines, working closely with WHO and industry. After careful evaluation of the antigenic and genetic characteristics of influenza viruses that are circulating and infecting humans across the globe and the ability of current vaccines to protect against these viruses, WHO makes recommendations on the composition of the influenza vaccines for use in the upcoming influenza season. These recommendations are taken into account by national vaccine regulatory agencies, such as FDA,

and vaccine manufacturers as they consider the vaccine composition for the upcoming season. WHO usually makes its vaccine strain recommendations in late February for the upcoming influenza season in the Northern Hemisphere and in September for the upcoming influenza season in the Southern Hemisphere. The recommendations must be made months in advance of the next influenza season because of the time required for manufacturing, testing, lot release, and distribution of a very large number of vaccine doses consisting of antigens derived from three or four different influenza virus strains.

FDA's Role and the Manufacturing Process

WHO recommendations resulting from the technical consultations described above provide a guide to national public health authorities and vaccine manufacturers for the development and production of influenza vaccines for the upcoming influenza season. In the United States, FDA is responsible for regulating vaccines. In this role, FDA brings together public health and influenza disease experts to recommend which influenza virus strains should be included in FDA-licensed vaccines. FDA convenes its Vaccines and Related Biological Products Advisory Committee (VRBPAC) each year, typically in late February or early March, usually within a couple of weeks of the WHO consultation on influenza vaccine composition.

The VRBPAC considers the recommendations made by the WHO regarding the composition of influenza vaccines for the upcoming influenza season in the Northern Hemisphere. The committee also reviews information regarding viruses that have caused human illness in the previous year, how these viruses are changing, and disease trends. The information considered in the review is provided in large part by CDC and WHO laboratories throughout the world. Based

on the data available at the time of the meeting, the advisory committee makes a recommendation for the composition of influenza vaccines licensed by FDA for use in the United States during the upcoming season.

Once the strains are selected, candidate influenza viruses that are adapted for high growth are generated and accepted by WHO collaborating centers. The candidate influenza viruses are provided to the licensed vaccine manufacturers to generate the "seed viruses" for manufacturing their influenza vaccines. The manufacturing demands for influenza vaccines are substantial; there is no other vaccine that has to be produced, FDA-approved, and distributed every year across the United States within a six-month time frame. This influenza season, more than 150 million doses were manufactured. The manufacturing timelines are tight and the process of producing influenza vaccine involves many sequential steps and overlapping processes. Even with technologic advancements, each of these steps and processes still requires time to complete. Given the yearly need for a new vaccine, there is limited flexibility in the timelines for influenza vaccine production and availability.

Manufacturing of each antigen to be included in the vaccine occurs sequentially over several months, usually from December (produced at risk by the manufacturer before the strain recommendations are made) until late May. In parallel with vaccine manufacturing, FDA develops and calibrates reagents which are provided to the vaccine manufacturers and our regulatory counterparts throughout the world. Manufacturers and FDA use these reagents to test the vaccines for potency and identity before FDA approves the new formulation of the licensed seasonal influenza vaccines for U.S. distribution. The vaccines are formulated into standard

dosages, filled and finished by the manufacturers into final containers such as vials, syringes, and sprayers. Manufacturers submit their vaccine testing results, along with samples from each lot, to FDA for "lot release." As FDA releases lots, the manufacturers can make these lots commercially available throughout the United States. Typically, FDA approves the updated seasonal influenza vaccines with new labeling by the end of July. Every year, FDA begins working with manufacturers at the earliest stages of influenza vaccine development, and we continue to assist them throughout the production phase. During this period, we engage the companies on technical and manufacturing issues and conduct biennial facility inspections.

2014-2015 Influenza Season

Influenza viruses are constantly changing, and variants can appear at any time, including during the vaccine manufacturing period. There is always the possibility of a less-than-optimal match between the influenza virus strains that end up predominating in the influenza season and those covered by the vaccine. This occurred in the current influenza season.

Since September, most of the influenza A (H3N2) viruses found in patients with influenza in the United States are different (drifted) from the H3N2 vaccine virus component, suggesting that the vaccine's ability to protect against the drifted virus will be reduced. At the time the strain selection recommendation was made in late February 2014, the majority of cases of influenza disease were caused by influenza A (H1N1), not influenza A (H3N2), and the drifted H3N2 viruses had not been detected in the United States. These drifted H3N2 viruses were not detected until March 8, 2014, and were uncommon. Since that time, the drifted H3N2 viruses gradually increased as a proportion of H3N2 viruses isolated over the ensuing months and have

caused a majority of influenza cases this season. WHO made its recommendations for the 2015 Southern Hemisphere influenza vaccine on September 25, 2014, by which time these drifted H3N2 viruses were common, prompting a recommended change in the upcoming Southern Hemisphere vaccine composition. At this point, because of the time required to manufacture influenza vaccine, it would not have been possible to make adequate amounts of influenza vaccine containing the drifted H3N2 virus in time for our peak influenza season, which usually occurs between December and February.

This situation stands in contrast to the emergence of pandemic H1N1 virus in the spring of 2009. By May 2009, the pandemic virus had spread rapidly throughout the world, resulting in thousands of cases in the United States, and WHO had made a candidate vaccine recommendation. WHO declared an influenza pandemic on June 11, 2009. Although tremendous efforts toward manufacturing of H1N1 pandemic vaccines began in the spring, it was not until late October 2009 that the first doses of this vaccine became available, with the bulk of the supply becoming available only in the December to January time frame. Although the production of a supplemental H1N1 vaccine in 2009 demonstrated flexibility to adapt to rapidly changing circumstances, the time required for manufacturing, testing, release, and distribution of the vaccine could only be compressed so much. As described in more detail in the next section, since 2009, significant advances have been made to broaden influenza vaccine manufacturing approaches in an effort to further compress timelines.

Even when a drifted virus appears later in the year, as it has done the current season, vaccination is still important to prevent disease and minimize the public health burden of influenza.

Influenza vaccines contain three or four influenza viruses (depending on whether the vaccine is a trivalent or quadrivalent formulation), so that even when there is a less than ideal match or lower effectiveness against one virus, the vaccine may protect against the other viruses.

Progress in Influenza Vaccine Manufacturing

In spite of the difficulties inherent in preparing influenza vaccines, we have made progress in our preparedness efforts in collaboration with the Biomedical Advanced Research and Development Authority (BARDA), CDC, NIH, and other stakeholders. For example, new influenza vaccines have been licensed since 2009, including cell-based influenza vaccines, recombinant protein vaccines, and quadrivalent influenza vaccines. Cell-based and recombinant protein influenza vaccines provide an alternative to the traditional egg-based process of manufacturing, and provide the potential for a faster start-up of the vaccine manufacturing process. FDA licensed the first cell-based influenza vaccine, Flucelvax, manufactured by Novartis, in November 2012, and the first recombinant influenza vaccine, FluBlok, manufactured by Protein Sciences, in January 2013. In addition, FDA has licensed quadrivalent influenza vaccines from four different manufacturers since 2011. Prior to the licensure of quadrivalent vaccines, all FDA-licensed vaccines were intended to protect against two influenza A strains and one influenza B strain. The quadrivalent vaccines are intended to protect against two influenza A strains and two influenza B strains, representing the two B lineages that often are circulating in any given season. To enhance pandemic preparedness, in 2013, FDA licensed an adjuvanted H5N1 vaccine, manufactured by GlaxoSmithKline Biologicals, and has worked with U.S. Government partners and manufacturers to facilitate the development of candidate vaccines directed at H7N9 influenza.

Surveillance efforts are more extensive than ever before and offer the potential for early detection of emerging influenza viruses. The number of candidate vaccine virus strains available to manufacturers has increased greatly over the last few years, providing them with more options to increase vaccine yields. FDA, in conjunction with BARDA, CDC, and NIH, continues efforts to develop high yield candidate vaccine strains, as well as more modern, faster methods to measure vaccine potency and sterility. To further address the challenges presented by the constantly changing nature of influenza viruses, scientists in government laboratories, academic institutions, and vaccine manufacturers are working to develop new-generation vaccines that might be longer lasting and provide broader protection against drifted strains. Although these vaccine development efforts are still in early stages, some may have potential to increase and broaden protection against influenza. FDA will continue to work with U.S. Government partners, manufacturers, and other stakeholders to facilitate development of new vaccines and identify methods that have the potential to speed the manufacturing process for existing vaccines. Our goal is to better protect the American public, including those at higher risk of complications from influenza.

Mr. MURPHY. Thank you.

Now, Dr. Robinson, you are recognized for 5 minutes.

STATEMENT OF ROBIN A. ROBINSON

Dr. ROBINSON. Good morning, Chairman Murphy, Ranking Member DeGette, and distinguished members of the subcommittee. Thank you for the opportunity to speak with you today. I am Dr. Robin Robinson, Director of the Biomedical Advanced Research and Development Authority, and Deputy Assistant Secretary for Preparedness and Response, as well as a former developer of influenza vaccines in industry.

BARDA is the Federal Government agency mandated to support advanced research and development, and procurement of novel and innovative medical countermeasures such as vaccines, therapeutics, diagnostics, and medical devices for the entire Nation to address the medical consequences of manmade and naturally occurring threats like the H1N1 pandemic, the 2013 H7N9 influenza outbreak, and the current Ebola epidemic.

Pandemic influenza is one of our primary concerns. We understand that preparedness for pandemic influenza is directly tied to seasonal influenza. Medical countermeasures for seasonal influenza underpin the vaccines, antivirals, and diagnostics used for pandemic influenza. BARDA has invested in the advanced development of medical countermeasures that have utility for both seasonal and pandemic influenza preparedness.

BARDA transitions medical countermeasures from early research and development at NIH, into advanced development toward FDA approval and potential procurement. BARDA has funded and successfully managed the advanced development of more than 60 medical countermeasures for pandemic influenza. More than 20 of these medical countermeasures for influenza have been FDA approved, with 6 receiving approval in the last 3 years, as Dr. Midthun indicated. Additionally, BARDA developed and procured vaccines and antivirals used in the 2009 H1N1 pandemic, and stockpiled vaccines for preparedness against H5N1 and H7N9 viruses. BARDA, through partnerships with NIH, CDC, FDA, industry, and academia, has met and overcome many but not all of the challenges inherent to making medical countermeasures associated with seasonal and pandemic influenza. Specifically, BARDA, with our partners, has made major progress in the following pandemic areas.

First, modernization of influenza vaccine manufacturing through the development and licensure of new cell- and recombinant-based influenza vaccines, and antigen-sparing pandemic vaccines with adjuvants towards meeting our strategic goal of more and better influenza vaccines sooner. These new vaccines were part of our successful H7N9 response in 2013.

Second, shortening influenza vaccine manufacturing time by weeks, effected through the Influenza Vaccine Manufacturing Improvement initiative, as recommended by PCAST, to optimize the generation of high-yielding vaccine seed strains, and alternative potency and sterility assays. Many of these improvements, such as biosynthetic technology, were employed during the H7N9 vaccine response in 2013, which was the fastest on record.

Third, establishment and maintenance of pre-pandemic influenza vaccine stockpiles for H5 and H7N9 viruses that may be used to immunize tens of millions of persons at the onset of an influenza pandemic with these viruses.

Fourth, and last, multi-fold expansion of domestic pandemic influenza vaccine production capacity, afforded by retrofitting of older manufacturing plants, building new state-of-the-art manufacturing facilities for making 21st century influenza vaccine, and establishing three centers for innovation and advanced development and manufacturing, with rapid, nimble, and flexible manufacturing capabilities through public-private partnerships with industry.

The new national infrastructure responded in 2013 to the H7N9 outbreaks, and today, in the Ebola epidemic. Despite these significant accomplishments, our pandemic preparedness work is not over. Making a more effective influenza vaccine remains a significant scientific challenge. Indeed, progress towards more effective influenza vaccines has been noted in recent years, but much more is needed.

Going forward, there is reason for hope that more effective influenza vaccines may be within our grasp. The discovery of new influenza viral targets within the last 4 years has renewed interests and efforts to develop new universal influenza vaccine candidates.

Developing more effective pandemic influenza vaccines is one of our top priorities, and BARDA will support new methods based on evolutionary biology that may help forecasting and selection of new seasonal and pandemic influenza vaccine strains.

In parallel, we are launching this month an initiative to support advanced development of new, more effective influenza vaccine candidates that may elicit greater, broader, longer immunity in all populations against divergent influenza virus variants, and that may serve as primers for pandemic influenza vaccines.

In conclusion, influenza viruses with pandemic potential continue to evolve and change, infect animals and man, and pose significant threats to global and domestic public health. This year's limited seasonal influenza vaccine effectiveness, and the arrival of the first human case of H7N9 virus in North America underscore our urgent need to complete this mission. To be better prepared, our Nation must continue to invest in domestic pandemic preparedness, and work with key global partners.

I thank you for this opportunity to discuss how we can be better prepared for seasonal and pandemic influenza, and I look forward to your questions.

[The prepared statement of Dr. Robinson follows:]

Written Testimony
Committee on Energy and Commerce
Subcommittee on Oversight and Investigations
United States House of Representatives

"Seasonal and Pandemic Influenza Preparedness: The Biomedical Advanced Research and Development Authority's Response"

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

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

For Release on Delivery
Expected at 10:00 AM
Tuesday, February 3, 2015

Good morning, Chairman Murphy, Ranking Member DeGette, and distinguished Members of the Subcommittee. Thank you for the opportunity to speak with you today about our Government's seasonal and pandemic preparedness and response medical countermeasure (MCM) efforts and challenges. I am Dr. Robin Robinson, Director of the Biomedical Advanced Research and Development Authority (BARDA) and Deputy Assistant Secretary to the Assistant Secretary for Preparedness and Response (ASPR) of the Department of Health and Human Services (HHS).

BARDA is the Federal Government Agency mandated to support advanced research and development and procurement of novel and innovative MCMs such as vaccines, therapeutics, antiviral and antimicrobial drugs, diagnostics, and medical devices for the entire Nation to address the medical consequences of man-made chemical, biological, radiological, and nuclear (CBRN) agents of terrorism and naturally-occurring and emerging threats like the H1N1 pandemic, last year's H7N9 influenza outbreak, and the current Ebola epidemic.

By supporting advanced research and development of MCM candidates, BARDA addresses the medical consequences of these threats and bridges the gap between early research and development and Food and Drug Administration (FDA) approval and potential procurement of MCMs for novel threats. Advanced development includes critical steps needed to transform a candidate to a product that is ready to use. These steps include optimizing and validating manufacturing processes such that products can be made at commercial scale; optimizing product formulations, storage, and product longevity and effectiveness; creating, optimizing, and validating assays to assure product integrity; conducting late-stage clinical safety and efficacy studies; and carrying out pivotal animal efficacy studies that are often required for approval of

CBRN MCMs. Since 2006, BARDA has funded and successfully managed the advanced development of more than 150 MCMs for CBRN threats and pandemic influenza. Eight of these products have received FDA approval in the last two years alone, and twelve of these products have been made available for use under Project BioShield. BARDA has supported the development of 18 influenza medical countermeasures since 2007 that were used in the 2009 H1N1 pandemic and stockpiled for avian influenza H5N1 and H7N9 outbreaks.

Seasonal influenza occurs every year. Periodically, however, novel influenza virus strains for which there is little human immunity emerge and these can cause global pandemics like the H1N1 2009 pandemic, or worse the pandemic of 1918. Because influenza viruses mutate as they traffic and reassort among birds, swine, and man primarily, achieving protection against seasonal influenza viruses is a significant challenge. Means to control and address the medical and public health consequences of influenza include social distancing, proper hygiene practices, vaccination, antiviral drugs, and diagnostics. In the last decade we have been reminded how complex management of seasonal and pandemic influenza are both globally and nationally. These reminders have included the following:

- the reemergence of H5N1 avian influenza in 2003 in Vietnam with high mortality in humans and spread from Southeast Asia to the Middle East through 2009,
- the shutdown of one of the two major influenza vaccine suppliers to the U.S. in 2004-2005,
- the rapid emergence of drug resistant H1N1 mutants to influenza neuraminidase inhibitors in 2008-2009,
- the H1N1 pandemic of 2009-2010,

- the emergence of seasonal H3N2 virus variants in 2012 in the Midwest primarily affecting children,
- the emergence of H7N9 avian influenza viruses in China in 2013 that were highly virulent for humans, and
- the mismatches of seasonal influenza vaccines with circulating H3N2 viruses in 2012-2013 and again this year.

The potential of the H5N1 virus to become a severe influenza pandemic resembling the 1918 pandemic led to the issuance and implementation of the *National Strategy for Pandemic Influenza* (2005) and sparked important efforts to develop new influenza medical countermeasures, establish vaccine and antiviral drug stockpiles, and expand domestic vaccine manufacturing. The lessons learned from the H1N1 pandemic resulted in the President's Council of Advisors on Science and Technology's (PCAST) *Report to the President on Reengineering the Influenza Vaccine Production Enterprise to Meet the Challenges of Pandemic Influenza* (2010) recommending improvements in virus surveillance, vaccine research and development, and influenza vaccine manufacturing. HHS reexamined and implemented revised plans to develop new influenza vaccines, antiviral drugs, and diagnostics; to assess the size, composition, and usage of influenza vaccine and antiviral drug stockpiles, and to expand our domestic influenza vaccine manufacturing infrastructure and capacity. The common thread throughout these preparedness and response plans is that seasonal and pandemic influenza are inextricably interwoven; what we do in one area directly affects what we do in the other.

For influenza vaccines, HHS set as a goal "more and better influenza vaccines sooner" meaning that we need more effective vaccines available in large quantities for seasonal and pandemic influenza faster. For influenza antiviral drugs, we looked for new drugs focused on new viral and host targets less vulnerable to drug resistance and that would be effective against severe hospitalized cases of influenza. For influenza diagnostics, we supported development of more rapid and sensitive diagnostics for point-of-care clinical settings and high throughput diagnostics for State, national, and commercial laboratories to increase capacity, sensitivity, and rapidity.

HHS, as integrated and coordinated Federal Agencies – NIH, CDC, FDA, ASPR, ASH, and BARDA- has partnered with industry and academia to address these seasonal and pandemic influenza challenges. ASPR coordinates overall HHS and government-wide influenza pandemic preparedness and response strategies and action plans in concert with the seasonal influenza activities managed out of the National Vaccine Program Office in the Assistant Secretary for Health. BARDA is directly responsible for working with industry and Federal partners to: (i) support advanced development of new influenza vaccines, antiviral drugs, and diagnostic devices leading to FDA approval for the U.S. market; (ii) improve influenza vaccine manufacturing resulting in greater vaccine production yields and availability sooner; (iii) build and maintain stockpiles of pre-pandemic influenza vaccines for the critical workforce and antiviral drugs at the Federal and State levels; and (iv) expand domestic and global pandemic influenza vaccine manufacturing infrastructure and capacity multifold.

BARDA's pandemic influenza mission is not yet completed. Although the recent introduction of quadrivalent and high-dose seasonal influenza vaccines by vaccine manufacturers represents

incremental progress towards more effective influenza vaccines, there remain significant technical challenges before a substantially better influenza vaccine is available. The discovery of new viral targets within the last four years has renewed interest and efforts to develop the long-sought-after "universal" influenza vaccine.

Because of the close scientific and technical connections between seasonal and pandemic influenza, developing better influenza vaccines is a top priority for BARDA. BARDA's program to develop better influenza vaccines includes methods based on the field of evolutionary biology that may augment existing methods to forecast and select new seasonal and pandemic influenza vaccine strains. In parallel, we are launching this year an initiative to support advanced development of new influenza vaccine candidates that may elicit greater and broader immunity for all populations, longer duration of immunity, greater cross-protection against influenza virus variants, and that may serve as primers for pandemic influenza vaccines. To complement our goal to develop better influenza medical countermeasure, BARDA is adding immunotherapeutics or antibodies to our antiviral drug portfolio as a new approach to treat severe cases of influenza.

BARDA Accomplishments in Influenza Medical Countermeasures

Since December 2005, HHS has been supporting fundamental medical countermeasures for seasonal and pandemic preparedness activities. Following the release of the Department's *Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Review* (2010) and the aforementioned PCAST report (2010), HHS made a mid-course adjustment and took steps to efficiently execute the pandemic influenza preparedness priorities enumerated in the review and report.

HHS has made significant progress improving vaccines and manufacturing technologies. Specifically, BARDA has partnered with industry to achieve the following:

- Modernization of influenza vaccine manufacturing systems through the development and licensure of new cell- and recombinant-based influenza vaccines as well as antigen-sparing vaccines
    - Flucelvax (licensed 2012), the first cell-based seasonal influenza vaccine in the U.S.
    - FluBlØk (licensed 2013), the first recombinant-based seasonal influenza vaccine in the U.S., and
    - Q-Pan H5N1 vaccine (licensed 2013), the first adjuvanted pandemic influenza vaccine in the U.S.
- With NIH, CDC, and FDA, we launched the Influenza Vaccine Manufacturing Improvement (IVMI) initiative, as recommended by PCAST to optimize the generation of high yielding vaccine seed strains and alternative potency and sterility assays, to expedite influenza vaccine availability. The IVMI initiative improvements cut weeks off the vaccine manufacturing process and increased production yields
- Establishment and maintenance of pre-pandemic influenza vaccine stockpiles for H5N1 and H7N9 viruses with pandemic potential to rapid immunization of the critical workforce at the onset of an influenza pandemic; in parallel BARDA and CDC developed and implemented the Influenza Risk Assessment Tool (IRAT) in 2010 to inform the composition and prioritization of vaccines in this stockpile;
- Multi-fold expansion of domestic influenza vaccine production for pandemic preparedness by retrofitting older manufacturing plants (2007-2011) and building new state-of-the art, award-winning new manufacturing facilities (2009-2012) through BARDA's public-private partnerships with industry;

- Establishment of a national infrastructure to rapidly develop, manufacture, and test new influenza vaccines and medical countermeasures for emerging infectious diseases, such as Ebola. This infrastructure responded in 2013 with the development, production, testing, and stockpiling of H7N9 influenza vaccines and more recently Ebola vaccine and monoclonal antibody therapeutic candidates in 2014-2015. BARDA's national response infrastructure is comprised of the following programs:
    - Nonclinical Studies Network (2011) comprised of 17 laboratories able to perform animal testing;
    - Centers for Innovation in Advanced Development and Manufacturing (CIADM) (2012) comprised of three (3) government-industrial-academic consortia to develop and manufacture MCMs for CBRN threats routinely and in an emergency for pandemic influenza and emerging infectious diseases such as Ebola;
    - Fill Finish Manufacturing Network (FFMN) (2013) comprised of four (4) Contract Manufacturing Organizations to provide aseptic filling of medical countermeasures for CBRN threats, pandemic influenza, emerging infectious diseases, and possibly U.S. drug shortages (pilot program between FDA and BARDA);
    - Clinical Studies Network (2014) comprised of five (5) Clinical Research Organizations to provide clinical evaluation of medical countermeasures as needed for man-made and natural threats including Ebola currently.

The CIADMs and FFMN fulfilled the PCAST Report recommendation to expand and improve vaccine manufacturing capacity to meet the national goal of making the first dose of pandemic influenza vaccine available within 12 weeks of pandemic onset and to

ensure that sufficient quantities are available to meet national demand in less than six (6) months.

- Establishment of a global vaccine manufacturing infrastructure with the World Health Organization in 2006 in eleven (11) developing countries to make pandemic influenza vaccines and vaccines for other diseases resulting in four licensed influenza vaccines and a current capacity able to produce more than 300 million doses of pandemic influenza vaccine;
- Development of novel influenza antiviral drug candidates for treatment of influenza leading to the FDA approval (2014) of the first intravenously-administered, single dose influenza antiviral drug - Rapivab (peramivir), which was accessible under EUA during the 2009 H1N1 pandemic;
- Establishment of Federal and State stockpiles of influenza antiviral drugs and assistance to the CDC's Strategic National Stockpile in the maintenance of these stockpiles;
- Development and FDA clearance (2012) of a PCR-based rapid point-of-care clinical diagnostic (Simplexa) for detection of influenza and respiratory syncytial viruses. Similarly BARDA and CDC jointly developed rapid simple diagnostics for detection of seasonal and H5N1 viruses in point-of-care (POC) settings by health care providers and complex diagnostics for high throughput settings in State health and commercial clinical laboratories. and
- Development and FDA clearance (2012) of next generation portable ventilators (Aura).

HHS Influenza Improvements in Action – H7N9 Response (2013)

The HHS response to the H7N9 avian influenza outbreaks exemplified Federal agency cooperation and public-private partnerships with industry building upon lessons learned from the 2009 H1N1 pandemic. The HHS interagency IRAT process determined that the risk from H7N9 was significant, and that it would be prudent to stockpile vaccine. BARDA played a key role in these HHS efforts including utilization of new cell- and recombinant-based flu vaccines developed with BARDA support. Secondly, H7N9 vaccine seeds using biosynthetic methods were developed by Novartis with BARDA support as a result of the technology derived from the HHS IVMI initiative to provide vaccines faster. Finally, the Novartis CIADM in Holly Springs, North Carolina played a major role in the development, manufacturing, clinical testing, and stockpiling of H7N9 vaccines in record time.

BARDA and the Future of Influenza Medical Countermeasures

BARDA is working with NIH to foster collaborations with academia and industry in pursuit of more effective influenza vaccines. New evolutionary biology methods such as antigen cartography may be able to predict influenza virus evolution better and understand immune responses to the influenza viral hemagglutinin (HA) proteins from genetically-distinct viruses better. By generating specific and random influenza virus mutants to seasonal and pandemic influenza viruses, the evolutionary trend for new virus strains may be obtained and thus may inform vaccine strain selection. Using these results, future vaccine candidates may be designed using this forward-looking information and provide pre-emptive vaccination through what is called back-boost vaccine immunity. BARDA is supporting such studies to inform the

composition of pre-pandemic H5N1 and H7N9 vaccine stockpiles, as well as seasonal human vaccine strains.

The discovery in 2010-2011 that the conserved regions or the stalk of the influenza hemagglutinin protein, which is the major immunogenic component of influenza vaccines, could elicit protective immunity across many influenza virus strains has brought renewed interest into the development of new types of influenza vaccines or so-called "universal influenza vaccines" and monoclonal antibodies as new immunotherapeutics. Several current vaccine candidates including a chimeric HA stalk vaccine candidate are in early development supported jointly by BARDA and the NIH's National Institute of Allergy and Infectious Diseases (NIAID). BARDA is launching a new advanced development program for more effective influenza vaccines this month. Based on these same discoveries, BARDA is starting a new program to support the advanced development of influenza immunotherapeutics to treat severe hospitalized cases of influenza.

Conclusion

Influenza and other emerging infectious diseases with pandemic potential continue to mutate, evolve, and infect animals and humans, posing continued significant threats to global public health and to the United States. Together with our Federal and industry partners, we have made great strides towards pandemic influenza preparedness. Our Nation must continue to invest in domestic pandemic preparedness efforts and work with key global partners to prepare for, prevent, detect, and respond to emerging pandemic threats. This year's limited seasonal influenza vaccine effectiveness and the arrival of the first human case of H7N9 virus in North America highlight our urgent need together with industry and academic partners to make better seasonal and pandemic influenza vaccines, antivirals, and diagnostics. ASPR and BARDA are

prepared to meet those challenges and provide resources, expertise, and technical assistance for these and other promising investigational vaccine and therapeutic candidates.

Mr. MURPHY. Thank you, Dr. Robinson.
Dr. Fauci, you are recognized for 5 minutes.

STATEMENT OF ANTHONY S. FAUCI

Dr. FAUCI. Mr. Chairman, Ranking Member DeGette, members of the committee, I appreciate the opportunity to discuss with you today very briefly the role of the National Institute of Allergy and Infectious Diseases in research addressing both seasonal and pandemic influenza.

[Slide shown.]

As shown on this slide, the NIH research agenda is really based on the traditional approach that the NIH has taken with all diseases; namely, fundamental basic research, clinical research, and field research, the provision of research resources both to the academic community, as well as to the biotech and pharmaceutical companies. The endgame is to ultimately produce interventions in the form of diagnostics, therapeutics, and vaccines. You have heard about the diagnostics and therapeutics. We can talk about them a little bit later. I want to focus the remainder of my remarks on a subject of obvious importance; namely, the development of influenza vaccines.

[Slide shown.]

Traditionally, the classic what we call platforms, or the way you develop the vaccine, have been based on growing the virus itself either in eggs, which is somewhat cumbersome, or more recently using it in cell lines, which are a bit more predictable. You either have a live attenuated vaccine or an inactivated vaccine, and that has been the traditional approach towards vaccines. It is cumbersome, it takes a long period of time because you have to grow the virus.

[Slide shown.]

Our researchers, both at the NIH and our grantees and contractors, over the last several years have been attempting, with some success, to make a conversion to what we call a recombinant DNA technology, molecular-based approach that would obviate the need to actually continue to grow the virus to make a vaccine. Several of these are illustrated on this slide. We don't have time to go into each and every one of them, but they are particularly suited to develop a vaccine that we are all hoping for, and that Dr. Burgess mentioned in his 5-minute remarks, and that is a universal influenza vaccine.

[Slide shown.]

This is the cover of a Nature Medicine article that I wrote with my colleague, Dr. Gary Nabel, the former director of the Vaccine Research Center, namely, how we can induce what I called unnatural immunity; namely, immunity that a normal vaccine induction or the virus itself doesn't induce, and that is broad protection against subsequent exposures to different types of influenzas that have a tendency to drift over a period of years, and sometimes to even shift, which gives us a pandemic.

[Slide shown.]

Now, the reason we can do this, and I just want to point out on this slide, on the lower right is a blown-up schematic of the influenza virus. The proteins that coat the outside are referred to as he-

magglutinin, and that is where we get the H for H3, H2, or H1. It is a designation of a major protein. The other one is N for neuraminidase. But notice how those proteins are clustered on the surface of the virus, so that what the immune system sees generally is just the top, what we refer to as the head or the bulb of that protein.

[Slide shown.]

If you look at this slide, that head is where most of the antibodies that protect you and me against influenza are made. That is the good news. The sobering news is that is a variable region, which tends to change as influenzas drift from season to season and change an awful lot when it goes to a pandemic.

If you look at the little stem, the thin part of that protein, that the immune system doesn't see very well, interestingly, we found out several years ago that that is the part—that is what we called highly conserved. It doesn't change from necessarily a Texas H3N2 to a different type, a Singapore or a variety of others. They stay the same, which means that if you can induce an immune response against that unchangeable one, you might be able to get what we call a broader reactivity.

[Slide shown.]

And over the last several years, we have made considerable progress as shown on this slide here, where a number of candidates have used molecular techniques to essentially show the body predominantly the part of that protein that doesn't change. And there are a number of ways of doing that. Instead of giving the body the entire virus, either killed or attenuated, by molecular techniques, you show the body only the part that you want it to respond to, unencumbered by the physical structures that don't allow the body to see it. And we now have done this in several candidates—in mice, in ferrets, and what we call phase one studies in humans—which means we know it is safe, we know it can induce the kind of response that is more broad. In collaboration with BARDA, we are now starting to produce that to go into larger trials. And as Dr. Burgess said, we are not there yet, but we are clearly many steps further than what we were the last time I testified before this committee.

So I will stop there and be happy to answer any questions.

[The prepared statement of Dr. Fauci follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

The Role of the National Institute of Allergy and Infectious Diseases in Research Addressing Seasonal and Pandemic Influenza

Testimony before the

House Committee on Energy and Commerce

Subcommittee on Oversight and Investigations

Anthony S. Fauci, M.D.

Director

National Institute of Allergy and Infectious Diseases

February 3, 2015

Mr. Chairman and members of the Committee, thank you for the opportunity to discuss the response of the National Institutes of Health (NIH) to the public health threats posed by seasonal and pandemic influenza. The National Institute of Allergy and Infectious Diseases (NIAID) is the lead NIH institute for conducting and supporting research on infectious diseases, including influenza.

For more than six decades, NIAID has made important contributions to the understanding of infectious, immunologic, and allergic diseases, from basic research on disease pathogenesis to applied research to develop diagnostics, therapeutics, and vaccines. NIAID has a dual mandate that balances research addressing current biomedical challenges with the capacity to rapidly respond to new threats from emerging and re-emerging infectious diseases.

Among these emerging and re-emerging infectious diseases are the occasionally unpredictable seasonal influenzas and the largely unpredictable pandemic influenzas. As we are well-aware, the strain of H3N2 influenza A that is circulating during the currently relatively severe influenza season is poorly matched to the H3N2 virus contained in this season's influenza vaccine. This divergence has contributed to a lower-than-usual level of vaccine effectiveness and to elevated influenza activity. Historically, in influenza seasons when novel H3N2 viruses have predominated, we have observed higher hospitalization rates and increased mortality.

This experience, together with the constant threat of pandemic influenza, underscores the importance of NIAID's longstanding commitment to influenza research as well as the need for a universal influenza vaccine that could protect people against numerous strains of influenza over multiple influenza seasons. NIAID has built on knowledge gained from past experiences with pandemic influenza—most recently, the 2009 H1N1 pandemic—to enhance the research

infrastructure that will enable our rapid response should another influenza virus with pandemic potential emerge. Critical to these efforts are NIAID's partnerships with academia and with biotechnology and pharmaceutical companies, and collaborations with other Federal organizations, particularly the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Office of the Assistant Secretary for Preparedness and Response (ASPR), including the Biomedical Advanced Research and Development Authority (BARDA), and the National Vaccine Program Office within the Department of Health and Human Services.

Seasonal and Pandemic Influenza

Each year in the United States, 15 to 60 million people experience symptomatic influenza illness, and more than 200,000 are hospitalized. Annual influenza-related deaths in the United States ranged from about 3,000 to 49,000 over a recent 30-year period. Very young children, pregnant women, people 65 years of age and older, and individuals with underlying chronic health conditions are particularly susceptible to severe outcomes of influenza, including death. As influenza circulates around the globe each year, the genes of the influenza virus mutate and sometimes reassort or exchange genes with other influenza strains; this causes proteins on the surface of the virus to undergo varying degrees of structural changes. These changes, which are usually small, accumulate over time to cause "antigenic drift" that allows an influenza virus to evade in part the protection people may have built up against influenza viruses due to previous influenza vaccinations or prior influenza exposure. Antigenic drift in human influenza viruses causes the changes in seasonal influenza viruses that we see from year to year, and it is the reason why, each year, we must re-evaluate which influenza virus strains should be included in

the seasonal influenza vaccine. Occasionally, more profound changes in the genetic makeup of the influenza virus lead to "antigenic shift," which results in larger changes in the structure of its surface proteins. Because the vast majority of the population typically does not have existing immunity against a virus that has undergone an antigenic shift, a pandemic can ensue, as we saw with 2009 H1N1 pandemic influenza. We must constantly address these small and large evolutionary changes in order to be prepared for both seasonal and pandemic influenza.

Annual influenza vaccination is the primary method to prevent seasonal influenza. Current manufacturing typically requires growth of influenza vaccine strains in eggs, a laborious and time- consuming process. Recently, the growing of virus in cell lines for certain influenza vaccines is somewhat of an improvement in vaccine production over growing the virus in eggs; however, it still requires the tedious process of growing the virus. Influenza vaccine technology of the future, based on research largely supported by NIAID, is employing modern molecular biological techniques to circumvent this outdated approach.

Basic and Clinical Research

NIAID has a longstanding commitment to basic and clinical research on influenza to better understand how influenza viruses replicate, stimulate immune responses, and evolve into new strains. Results from these research studies inform the design of new and improved influenza vaccines, diagnostic tools, and antiviral drugs applicable to both seasonal and pandemic influenza strains. Partnerships between government, academia, and the biotechnology and pharmaceutical industries are critical to speeding the development of these countermeasures.

NIAID supports efforts to gain basic understanding of how influenza strains emerge, evolve, and infect animals and humans. NIAID's Centers of Excellence for Influenza Research and Surveillance (CEIRS) Program is supporting domestic and international influenza researchers studying the factors that control the emergence and transmission of influenza viruses among animal reservoirs, and the immunological determinants of whether an influenza virus causes only mild illness or results in severe disease or death. The CEIRS Program continually monitors cases of animal and human influenza worldwide to rapidly detect and characterize viruses that may have pandemic potential, such as the avian influenza strains H5N1 and H7N9.

In addition, NIH scientists are characterizing human influenza infection through studies in healthy volunteers who are challenged under controlled conditions with influenza virus to gain a better understanding of the basic biology of human influenza infection. Information gained from these studies will include how much time elapses between a known exposure to influenza virus and the start of viral shedding (a sign of contagiousness), the onset and duration of influenza symptoms, and the development of an immune response. These investigations also provide a scientific basis for more rapid, cost-effective clinical trials to evaluate new influenza drugs or to determine the efficacy of candidate vaccines for both seasonal and pandemic influenza.

Diagnostics

NIAID supports research to design influenza diagnostics that are faster and more accurate, cost-effective, and portable than current diagnostic tools. NIAID has worked to develop diagnostic platforms capable of examining influenza viruses at the molecular level and rapidly identifying a wide variety of virus types and subtypes. With NIAID support, researchers are developing clinical assays to determine whether influenza viruses are sensitive to neuraminidase inhibitors, a

class of antiviral drugs that inhibit influenza virus replication. Rapid influenza diagnostics that allow healthcare professionals to quickly distinguish one strain from another at the point of patient care and to detect resistance to antiviral drugs would ensure that patients receive the most appropriate care.

Antiviral Therapies

Antiviral medications are an important tool to control influenza by treating infection and helping to prevent severe illness. The neuraminidase inhibitors oseltamivir (Tamiflu®), zanamivir (Relenza®), and peramivir (Rapivab™) are the three antiviral drugs recommended for the treatment of influenza in the United States. When administered within 48 hours of onset of illness, these drugs can reduce the duration and severity of illness. However, experience tells us that resistance to influenza antiviral medications can emerge, and new and better treatments are needed.

NIAID continues efforts to develop and test the next generation of influenza treatments, including broad-spectrum antiviral drugs. NIAID has supported antiviral candidates at various stages of the development pipeline; several have entered clinical trials supported by NIAID and its government and industry partners. For example, NIAID supported initial Phase I clinical studies of a novel neuraminidase inhibitor, peramivir, which was recently approved by the FDA to treat influenza infection in adults. This is the first neuraminidase inhibitor available in IV formulation. NIAID has advanced the development of additional next-generation neuraminidase inhibitors, as well as influenza RNA polymerase inhibitors and monoclonal antibodies targeting the critical influenza surface protein hemagglutinin (HA). Three NIAID clinical trials are underway to explore the effectiveness of novel influenza therapeutics in high-risk populations,

including human plasma containing high levels of anti-influenza antibodies, concentrated immunoglobulin with high levels of anti-influenza antibodies, and a "cocktail" of three licensed influenza antiviral drugs.

Vaccines

New Vaccine Development Technologies

As mentioned above, antigenic drift and shift create significant challenges for those who must forecast which influenza virus strains are the most suitable targets for seasonal vaccine development. One way to address these challenges is to create flexible manufacturing processes that could respond rapidly to emerging seasonal or pandemic influenza strains. NIAID is pursuing technologies that could increase the efficiency of vaccine production and shorten manufacturing times. NIAID and industry partners have made progress in moving from the current egg-based, and to some extent cell-based, influenza vaccine production methods to recombinant DNA manufacturing that could be rapidly mobilized with the emergence of a pandemic virus. NIAID also has participated in the Influenza Vaccine Manufacturing Improvement Initiative in collaboration with ASPR/BARDA, CDC, FDA, and vaccine manufacturers. As part of this effort, NIAID is supporting accelerated and flexible vaccine production through development of novel assays, improved influenza strain selection, and optimized high-yield influenza virus vaccine strains.

NIAID has a longstanding vaccine clinical trials infrastructure, the NIAID Vaccine and Treatment Evaluation Units (VTEUs), ready to test vaccine produced through both new and traditional influenza vaccine manufacturing platforms. When NIAID, in close coordination with

CDC, BARDA, and FDA, moved rapidly to respond to the 2009 H1N1 influenza pandemic, the VTEUs conducted pivotal trials of 2009 H1N1 pandemic influenza vaccine. These studies determined the safety and appropriate dose of the vaccine to induce a predictably protective immune response in normal adult volunteers as well as in high-risk populations such as children, pregnant women, the elderly, and people who are immunocompromised.

Universal Influenza Vaccines and Other Vaccine Approaches

NIAID also invests in a major effort to develop a "universal" influenza vaccine that induces a broad and potent immune response to the common elements of the influenza virus that change very little from strain to strain. A universal influenza vaccine potentially could provide protection against numerous strains of influenza, including those that drift or even shift, such that protection could be sustained over multiple seasons. Advances in our understanding of the structure and immunological characteristics of hemagglutinin (HA) —a protein on the surface of the influenza virus that is targeted by the protective effect of the immune system—have shed light on the basic science behind universal influenza development. Using advanced genetic and structure-based technologies, scientists have determined that most antibodies against the influenza virus target the "head" of the mushroom-shaped HA protein structure; the head of the HA protein is also the component of this important protein subject to the antigenic drift that necessitates the generation of a new influenza vaccine every season. In contrast, researchers have discovered that the "stem" or stalk region of the HA protein is relatively unchanged among different influenza strains. Given this stability, an immune response against this stem could elicit a broad immune response effective against multiple influenza strains. NIAID has intensified universal influenza vaccine research and development focusing on the HA stem region, and

NIAID intramural and extramural researchers are advancing several promising universal influenza vaccine concepts into early clinical trials.

NIAID, in collaboration with BARDA and CDC, is planning a Phase I clinical trial in the VTEU network to investigate the human immune response to HA stem-based universal influenza vaccines. CDC has generated seed virus constructs for two stem-based vaccines developed by NIAID-funded scientists, and BARDA has supported production of clinical lots of the vaccine. In addition, NIAID Vaccine Research Center (VRC) researchers have carried out several Phase I/II clinical trials of a potential universal influenza vaccine by assessing an initial, "prime" vaccination with influenza virus DNA vaccine followed by a "boost" with a conventional, licensed seasonal influenza vaccine to induce enhanced and broadly reactive antibody responses. The study investigators are now evaluating data from those trials. NIAID VRC scientists also have developed an HA-ferritin nanoparticle vaccine to improve the potency and durability of seasonal influenza vaccination. This approach has shown promise in animal models, and the VRC team is assessing the vaccine strategy for further development, including potential application to universal influenza vaccine design.

While pursuing multiple strategies to develop a universal influenza vaccine, NIAID-funded researchers also are pursuing complementary strategies to improve seasonal influenza vaccines. For example, researchers are developing alternative vaccine delivery systems; identifying additional vaccine components that could elicit universal protection; and assessing the contribution of adjuvants, vaccine additives that can help create a more vigorous immune response to a vaccine. NIAID research efforts are yielding important information about the influenza virus that we hope will lead to an effective universal influenza vaccine. It is not

possible to predict when a universal influenza vaccine may be available, and candidates will need to be rigorously evaluated over multiple influenza seasons to determine durability of protection. However, progress in recent years is encouraging.

Finally, NIAID continues its efforts to prepare for pandemic influenza including the potential for wider spread of emerging strains of avian influenza such as H5N1 and H7N9. For example, NIAID intramural scientists, in collaboration with BARDA and industry, are working to develop live attenuated vaccines against influenza viruses with pandemic potential. In addition, NIAID is supporting clinical trials to understand human immune responses to H5N1 and H7N9 vaccines. These efforts include collaborations with BARDA on studies in the elderly of the safety and immunogenicity of an inactivated H7N9 vaccine developed by Sanofi Pasteur, with and without two different stockpiled adjuvants. Such studies will help to determine "dose-sparing" strategies to maximize the supply of stockpiled vaccines for pandemic preparedness.

Conclusion

NIAID plays a critical role in the comprehensive efforts of the Federal Government to combat influenza by supporting basic and translational research to inform the development of new and improved influenza diagnostics, therapeutics, and vaccines. A major focus of these efforts is the development of a universal influenza vaccine that could provide long-lasting protection against multiple strains of influenza, including seasonal and pandemic influenza. As we face the current severe and widespread seasonal influenza epidemic, NIAID will continue its ongoing and productive collaborations with partners in government, academia, and industry to develop and test novel and effective influenza countermeasures.

Mr. MURPHY. Thank you.

I will now recognize myself for opening questions for 5 minutes.

But let me just start off, and I know that a lot of concerns about vaccines and autism. As a psychologist, I have seen many a child with autism. It is a deeply concerning problem with the families. Past publications have been discredited, and data was deemed fraudulent. Multiple studies said there is no link between developmental disorders such as autism and vaccines.

I want to ask each of you, do you agree, Dr. Schuchat? Dr. Midthun, do you agree? Dr. Robinson, do you agree? Dr. Fauci, do you agree? And—yes, you can say this verbally. Should parents have their children vaccinated? Dr. Schuchat?

Dr. SCHUCHAT. Vaccines save lives and are the best way for parents to protect their children——

Mr. MURPHY. Yes, right.

Dr. SCHUCHAT [continuing]. From vaccine-preventable diseases.

Mr. MURPHY. Dr. Midthun, yes or no? Yes?

Dr. MIDTHUN. Yes. I have three children, and they were all vaccinated on time with all the recommended vaccines.

Mr. MURPHY. Dr. Robinson?

Dr. ROBINSON. Absolutely.

Mr. MURPHY. Dr. Fauci?

Dr. FAUCI. Definitely.

Mr. MURPHY. OK. Dr. Schuchat, flu expert Dr. Andrew Pavia at the University of Utah School of Medicine said, "By April or May, there was good evidence of the drifted A/Switzerland strain. It wasn't clear it was going to be a dominant strain, but there was a pretty good hint, we probably would have chosen the vaccine differently." Dr. Schuchat, do you agree that there was good evidence of the drifted strain by, say, April or May of this last year?

Dr. SCHUCHAT. We were certainly keeping a close eye on this drifted strain last May, and that is when the CDC began to develop a candidate vaccine virus, but as you know, it can be very challenging to develop candidate vaccine viruses, and to take it from a candidate to all the way to production of vaccine, all the way to production of hundreds of millions of doses of vaccine.

Mr. MURPHY. But by May, there was evidence of a 17 percent mismatch. Do you think that 17 percent mismatch was a concern at that point, and were there any discussions about that at CDC?

Dr. SCHUCHAT. Yes, there were. In fact, in March, we started to reach out to the global community, the international WHO collaborating centers, when we saw the first handful of this drifted strain to ask others were they seeing it.

I think it is important to realize that strains emerge and can disappear, and in the spring, it is very difficult to know which ones will still be around in the summer or fall. We actually respond to these new drifted strains by working on candidate vaccine viruses, but it is very difficult with influenza to predict what strains will dominate, whether it is going to be an H3N2 year or a H1N1 year. And so we continue to go through the routine seasonal flu work while we are also developing the candidate vaccine virus——

Mr. MURPHY. Well, let me ask about this pattern. We have here, I am looking at the mismatch notes, by March there is about a 10 percent mismatch drift, by May, 17 percent. We understand by

September it was already up to 50 percent. Do we know in these gaps of April or June or July or August what those drift rates were? Was there a problem by those times that was being seen?

Dr. SCHUCHAT. Yes, we have information for the summer. It is important to remember that there is very limited influenza circulating here in the U.S. in the summer, and it takes off in the fall. That is one of the reasons we do global worldwide surveillance——

Mr. MURPHY. Sure, but right here——

Dr. SCHUCHAT [continuing]. And we have greatly increased the numbers there.

Mr. MURPHY. But here in September, a decision was made for the World Health Organization to change this for the Southern Hemisphere. And so I am wondering, because there are big gaps here, were there discussions between all your agencies that we ought to be doing something differently other than telling people to have some kind of an antiviral medicine?

Dr. SCHUCHAT. Thanks. I think it is important—Dr. Fauci talked about the idea of drift and the idea of shift, and I think the members remember in 2009 where, in the spring of 2009, we did decide it was important to go forward with a monovalent vaccine——

Mr. MURPHY. Right.

Dr. SCHUCHAT [continuing]. Against a pandemic. We think of pandemics as having catastrophic risk because they generally are defined by a new strain that the population has no protection against at all. It is so differing from——

Mr. MURPHY. But you could do that fairly quickly during that—the issue of the Swine—from 2009. Once it reached this level where we are now only 23 percent effectiveness, and about 12 percent for senior citizens, a high-risk group for death, for mortality and morbidity, why not move forward at this point with at least a monovalent strain for high-risk groups and high-risk geographical areas?

Dr. SCHUCHAT. The time between developing a candidate vaccine virus, which we started working on in May, and the ability to have a lot of doses is about 6 months. So it really wouldn't be available——

Mr. MURPHY. But you did it in 12 weeks in 2009.

Dr. SCHUCHAT. The large amounts of vaccine were only available in November in 2009, after having really started in May.

Mr. MURPHY. But you did it in a much shorter time, but not the 6 months. My point is, when you identify something that is going to have that level of mortality and morbidity, and it can be done in a short period of time, were your agencies talking with each other and saying—clearly, a decision was made in September, hey, for the Southern Hemisphere, we need to change that, but for the Northern Hemisphere it says let us keep going with what we have, recognizing that it is only effective for 1 out of 5 people and 1 out of 10 seniors. It seems to me that you need a different decision-making process.

Dr. SCHUCHAT. Thanks. I think another point that is important to make is the difference between the laboratory mismatch and the clinical protection. In 2003/04, we had a laboratory mismatch. It turned out that when we measured clinical protection, protection was about 50 to 60 percent in different populations. So seeing that

in the lab in that hemagglutinin inhibition testing that there is drift or that there is a difference between the strain and the vaccine, and the strains that are circulating, doesn't perfectly predict how the vaccines will work in practice. So I think it is very important to differentiate that decision to make a monovalent vaccine against a pandemic where we know there is not going to be the widespread protection because people haven't seen the strain before, and where it is a race against time in terms of the—although it is challenging with current technology, the value of trying to make a vaccine is worth it.

Mr. MURPHY. I am way over time. I need to——

Dr. SCHUCHAT. By which—OK.

Mr. MURPHY [continuing]. Pursue other members.

I recognize Diana DeGette for 5 minutes.

Ms. DEGETTE. Thank you very much, Mr. Chairman.

Well, following up on the chairman's question, Dr. Schuchat, would it be fair to say, and really yes or no would work here, would it be fair to say that the way we are going to be able to substantially reduce the time between when we identify a strain and developing the vaccine will be what Dr. Fauci is talking about, which is development of new platforms and ways to get the vaccine?

Dr. SCHUCHAT. Absolutely.

Ms. DEGETTE. Now, Dr. Fauci, I want to turn to you because, over the years, you have come and talked about the development of these vaccines. I remember when we had a hearing in this committee when we were trying to move from the egg to the cell vaccine. And now you say you have the cell techniques, but you also say that you are getting ready to go into larger clinical trials on these new platforms, is that correct?

Dr. FAUCI. That is correct, Ms. DeGette. The important point is that we really think that anything that needs to grow the virus——

Ms. DEGETTE. Right.

Dr. FAUCI [continuing]. And produce it just is a time sink. So that is the point that I made on the——

Ms. DEGETTE. Right.

Dr. FAUCI [continuing]. Slide.

Ms. DEGETTE. No, and we actually, even those of us who only took high school biology, understood that point.

Dr. FAUCI. Yes.

Ms. DEGETTE. So——

Dr. FAUCI. Yes.

Ms. DEGETTE [continuing]. Good work again. But what I want to know is now that you have done your phase 1 trials, and you are trying to move beyond that, what is your time frame for that?

Dr. FAUCI. Well, you know, it is going to really depend on, first of all, testing it in a season to show that even though you don't specifically have it against this particular strain, that it is covering that strain. So when you are trying to prove universality, you want to test it in a season in which it is a broader response. One of——

Ms. DEGETTE. Right.

Dr. FAUCI. Yes. One of——

Ms. DEGETTE. So would that be like next season——

Dr. FAUCI. Well, we——

Ms. DEGETTE [continuing]. Do you think?

Dr. FAUCI [continuing]. Actually are going to try now, in collaboration with BARDA, to make enough of that new concept to be able to test it——

Ms. DEGETTE. Test it in this season.

Dr. FAUCI [continuing]. In the following season.

Ms. DEGETTE. Dr. Robinson, you are——

Dr. FAUCI. Following season.

Ms. DEGETTE [continuing]. You are nodding your head, yes. Is——

Dr. ROBINSON. Yes, the following season.

Ms. DEGETTE. OK. So what can Congress do to help you with that? Do you need additional resources? What do you need to be able to start to expedite that research?

Dr. FAUCI. Well, I mean, obviously, you ask a scientist if they need resources, the answer is an automatic knee-jerk——

Ms. DEGETTE. Well——

Dr. FAUCI [continuing]. Of course we can do better with more resources, but we actually need your continued support to keep the focus on the need for this, because when we do these tests, remember, we don't have control over the companies that make the contracts with the various——

Ms. DEGETTE. Right.

Dr. FAUCI [continuing]. Health organizations that distribute this, but I think the focus that this committee has continually put on this has been very helpful to us.

Ms. DEGETTE. Now, in your written testimony, you talk about the difference between seasonal flu and pandemic flu. Can you briefly explain that to us?

Dr. FAUCI. So I mentioned in my oral testimony a few moments ago that influenza viruses tend to change slightly. We call that a drift.

Ms. DEGETTE. Right.

Dr. FAUCI. Right.

Ms. DEGETTE. Every season.

Dr. FAUCI. That is a little bit. Now, if it changes slightly, even if you don't get the vaccine match right, there is enough background immunity in the community against similar viruses that the vast majority of the population are not going to have a catastrophic outbreak where people would be completely unprotected.

Ms. DEGETTE. Right.

Dr. FAUCI. When you have an influenza that has what we call a shift, not a drift, that means major changes, so when you look at the general population, the overwhelming——

Ms. DEGETTE. Right. They don't have that.

Dr. FAUCI [continuing]. Majority don't have any background protection. So it is almost as if you are totally naive to this new——

Ms. DEGETTE. And that is what happened in——

Dr. FAUCI [continuing]. Virus.

Ms. DEGETTE [continuing]. 2009 and 2010.

Dr. FAUCI. Indeed. The bad news, it happened in 2009. The somewhat comforting news is that it wasn't a particularly virulent——

Ms. DEGETTE. Right. Exactly. And that is what we——

Dr. FAUCI [continuing]. Virus. So we——

Ms. DEGETTE [continuing]. Were worried about.

Dr. FAUCI [continuing]. Were lucky.

Ms. DEGETTE. So, Dr. Robinson, now, you said in your testimony that there remains significant technical challenges before a substantially better influenza vaccine is available, and I would assume that the biggest concern for both of you gentlemen, well, for all four of our witnesses, would be that if we don't develop that significantly better vaccine system, and we get a virulent pandemic flu, is that right, Dr. Robinson?

Dr. ROBINSON. That is right. I mean, as Dr. Fauci pointed out, we actually have new ways to actually make these vaccines by looking at a different portion of one protein. We normally make the vaccines against the hemagglutinin and our immunities to that, the head of that, and now we can actually look at the stalk which we are making these candidates. We may be able, that way, to protect against many different drifted strains and serve as a primer for a pandemic so that you have one dose of this, so you only need one dose of pandemic vaccines instead of maybe two.

Ms. DEGETTE. Yes, and so what we are concerned about, or what I am concerned about, what keeps me awake at night, is if we don't do enough, both Congress and also our research institutions, to be able to have that vaccine available if we get a virulent pandemic flu. Dr. Fauci?

Dr. FAUCI. So another important point besides the fact that all of the issues, the advantages of this universal flu vaccine, namely, molecular biology rather than growing——

Ms. DEGETTE. Right.

Dr. FAUCI [continuing]. The critical issue is if you—if we get it right, you could actually stockpile it.

Ms. DEGETTE. Right.

Dr. FAUCI. So we wouldn't have to worry about the chart that the chairman put up about it changing and trying to keep up with it——

Ms. DEGETTE. Right.

Dr. FAUCI [continuing]. Because if you stockpile it, you could stockpile it the same way you stockpile polio vaccine, measles vaccine, et cetera. That is really the endgame.

Ms. DEGETTE. Thank you. Thank you very much, Mr. Chairman.

Mr. MURPHY. Thank you.

Now recognize Mrs. Blackburn, vice chair of the full committee, for 5 minutes.

Mrs. BLACKBURN. Thank you, Mr. Chairman. And as I said earlier, I want to focus on measles because we are hearing so much about this. And bear in mind, I have a daughter who has two children. They are in kindergarten and pre-K, and I can tell you, and I am sure you all and your teams, are fully aware that a lot of the mommy blogs are focused on this issue right now. And it is a big issue with our constituents.

And, Dr. Schuchat, let me come to you first. I just want to be sure what the known knowns are about the measles virus. If you would elaborate for just a second. We are hearing 102 cases, that out of these only five had a vaccination against measles. Do you know what the rate is how they are affecting elderly as well as children? If you will give us just 1 minute on this.

Dr. SCHUCHAT. Yes, so far, there have been 102 people from 14 States that have developed measles in 2015. There are another 11 cases of measles from the end of 2014 that were linked to the Disneyland outbreak. Not all of the 102 cases this year are linked with Disneyland, but the majority are.

The majority of people in these outbreaks so far have not been vaccinated. Only a small number are known to have been vaccinated. Important to remember that there are about 20 million measles cases around the world each year, and so measles is literally a plane ride away. When it gets into communities like the United States now, in certain pockets where a lot of people are unimmunized, it has a chance to spread. And so that is why California is really working day and night to follow every lead and put an end to it there. And that is why the health departments in every State are really on alert right now.

Mrs. BLACKBURN. OK. Let me ask you this. As a physician, and a representative of our Nation's public health agency, if you are talking to a parent, should they be more fearful of the disease, measles, or the measles vaccine?

Dr. SCHUCHAT. Every parent wants their child to be healthy and safe, and I absolutely respect that. As a physician and as a public health expert, I can tell you the measles, mumps, rubella, or MMR, vaccine is very effective and very safe.

Measles can be serious, and I would hate for a parent to think that everything will be fine, and have a bad outcome with their child. So I strongly recommend people talk with their physicians and get the right information, but personally, I would definitely have my child vaccinated.

Mrs. BLACKBURN. Thank you.

Dr. Fauci, same question to you.

Dr. FAUCI. Same answer from Dr. Schuchat. There is no doubt, if you do a risk/benefit of the vaccine versus the disease, I think it is very, very clear that you have one of the most highly effective vaccines against any virus, and you have a highly contagious disease, measles, that can have serious complications, so to me it is really a slam dunk what the decision would be.

Mrs. BLACKBURN. So if it were your child or grandchild, you would say vaccinate?

Dr. FAUCI. Without a doubt, and I have done that with my three children.

Mrs. BLACKBURN. Excellent. Thank you, sir.

Dr. Robinson, I am going to let you off the hook today. I usually have quite a group of questions for you. And I do, I have some questions on Tamiflu and on the stockpile and the shortage, but as one of my researchers from Vanderbilt told me this weekend, we don't always get the flu right and had a way of terming how we go about looking at this. I am going to, in the interest of time, submit these and would love a response from you.

And I yield back.

Mr. MURPHY. Thank you. The gentlelady yields back.

Now Mr. Pallone is recognized. Thank you.

Mr. PALLONE. Thank you, Mr. Chairman. I wanted to start out with Dr. Midthun. I am concerned about the low flu vaccine rate for children. By November 2014, only 42 percent of children be-

tween the ages of 6 months and 17 years have been vaccinated for the flu, and I think we need to change this. And, of course, the measles outbreak raises more concerns about childhood vaccination. Yesterday, we mentioned that Ms. DeGette, Mr. Green, and myself called for a separate hearing on the outbreak, and the importance of vaccination to prevent the spread of measles.

I am sorry, actually, my question is of Dr. Schuchat. What can we do to increase childhood vaccination rates, both for the flu and for other infectious diseases?

Dr. SCHUCHAT. You know, I think that parents' decisions to vaccinate their kids are often related to their sense of the threat and their sense of the value of the intervention. And we are so fortunate in this country that our disease rates have been quite low, that many parents don't realize these diseases are still out there, and that if their children aren't vaccinated, they will come back. So with the measles outbreak, I think most parents who weren't vaccinating didn't realize measles was still around and could be dangerous.

In terms of the value of the intervention, it is important for parents to have all the information they need about the safety, the effectiveness, the risks, and benefits. It is important to me that parents know that the immunization system is deeply committed to transparency, to monitoring vaccine safety, to sharing information about risks when we determine them, and to updating our recommendations whenever there is new data. Right now, we know that the vaccines we are giving are saving lives and saving money. For each dollar we put in, we get about $10 back for the childhood immunization series.

So what we do to try to support and promote immunization is a strong public-private partnership between healthcare professionals, doctors and nurses, and pharmacists, and community groups and consumer groups, to get information where it is needed, when it is needed, in many different formats. We know that most people trust their doctors and nurses more than they trust me or other public figures, and so we really try to support the doctors, nurses, pharmacists, that are that frontline.

Mr. PALLONE. Well, thank you. Let me continue with you. I know that the flu activity began in early December, and continued to increase through the end of 2014. Has the flu activity peaked for this year, and what data do you evaluate to make that determination?

Dr. SCHUCHAT. We are well along in the season, but it is difficult to say whether there will be a long tail or not. In many areas it is flattening off but not deeply declining yet. And sometimes later in the season, we see another strain increase. We have had many seasons where one of the H1N1 or H3N2 starts off the season, and one of the B strains will be quite common later on. So we are not out of the woods. It is important for people to be thinking about this. And we particularly want people to know that if they develop flu-like symptoms, and they are pregnant or they are very elderly, or have other immuno-compromising conditions, early treatment with antivirals could be very helpful to them. So they should speak with their clinician.

Mr. PALLONE. All right, let me go back now. I did have a question of Dr. Midthun. The flu vaccine comes in different forms.

There is the high-dose shot recommended for seniors, a quadrivalent nasal spray recommended for young children, and a recombinant trivalent, I don't know if I am pronouncing it right, recombinant trivalent shot recommended for those with egg allergies. How do you communicate to different groups about the variety of vaccines, and can the greater number of options for vaccines increase the rates?

Dr. MIDTHUN. As you point out, there are a number of different options now, and what we try to do is really communicate clearly the information that we provide on our Web site in our package inserts as to what groups were studied and for which age groups the product is indicated. So, for example, the high-dose vaccine you were referring to was actually evaluated in individuals 65 years of age and older, and was shown to decrease the rate of influenza by 23 percent, relative to those who got the normal dose vaccine. And likewise, quadrivalent vaccines are now available for four different manufacturers; three are inactivated and one is the live attenuated. They are indicated for somewhat different groups across that spectrum, and again, that information is put forward.

The recombinant vaccine that you mentioned has only so far been evaluated and shown to be safe and effective in 18 years of age and above, and so again, our prescribing information will reflect that. But I think I should really turn to Dr. Schuchat because that is really the advisory committee on immunization practices, which is an advisory committee for the CDC that then recommends how these vaccines should be used.

Dr. SCHUCHAT. And just briefly, we recommend people get vaccinated with the vaccine that is available. And so while providers and pharmacists get all that information about the different types, it is much more important to get a vaccine than to worry about which one is there.

Mr. PALLONE. All right, thank you. Thank you, Mr. Chairman.

Mr. MURPHY. Thank you.

I now recognize the vice chairman of the subcommittee, and welcome aboard as vice chairman, Mr. McKinley of West Virginia.

Mr. MCKINLEY. Thank you, Mr. Chairman. Just a quick observation on this—what I have heard and read in your testimony and done a little research is, this whole process of designating which vaccine we are going to come up with in September just seems archaic. In fact, it seems more of a game of chance and probability. And by virtue of us continuing this process, erroneously now with this mismatch, we have 50,000 Americans who are going to die this year. Fifty thousand Americans. That is more than died in combat in Vietnam, over a decade of that warfare. And they are going to die because of a game of chance and probability.

I am just astounded by that. I wonder what better techniques can we use to predict ahead. And that leads me then to the second question perhaps, or maybe associated with that, is that the high-dose vaccine has been found to be 24 percent more beneficial to senior citizens, and you have a meeting coming up late in February and it is not on the agenda as a possibility for September. Could one of you explain just briefly why that is not on the agenda if it has been proven to be helpful for senior citizens?

Dr. SCHUCHAT. Yes. Let me answer sort of both parts. The high-dose vaccine is one of the licensed vaccines that is recommended, and the company that makes it doesn't make enough of it for all people 65 and over——

Mr. MCKINLEY. Um-hum.

Dr. SCHUCHAT [continuing]. But they have been increasing the production. So it is included in the September and February recommendations. The recommendations are really just which vaccines to—which virus strains to target, and then there are all these different formulations like high-dose.

The other thing I just wanted to comment on about is sort of the mismatch. I want to just point out that in the past 20 years, this is the fourth time that we have had an important mismatch between one of the circulating viruses and the vaccine and what dominates. So it is very disturbing when we have this and we have excess disease burden, but the vast majority of recommended strains have actually been on track. Even though, when we have a good match, a well-matched vaccine type, we have a lot of morbidity and mortality from influenza, and I think it is one of these diseases that we as scientists take very seriously, but the American public takes a bit for granted. So we wish that we had more people vaccinated each year, and that we wish that people who need to get the antivirals would get them early, but we have work to do in terms of the medical community and the public——

Mr. MCKINLEY. Thank you.

Dr. SCHUCHAT [continuing]. And in having them take——

Mr. MCKINLEY. Thank you, doctor. Is——

Dr. SCHUCHAT [continuing]. It seriously.

Mr. MCKINLEY. I want to build a little bit of background for the chairman and his chart. When it was discovered first in May, I guess it was, that—or March, there was some anomaly showing up. May, 17 percent, September, 50 percent. It was obvious there was a problem with it. So if I go back to Robinson's testimony, he said that the PCAST report recommended improving vaccine manufacturing to meet a national goal of making the first dose within 12 weeks. Now, yes, it would have taken to go to a national supply to go 6 months, which again, is a real concern about the production, and some of the techniques that we can use to reduce that—but if we could have produced a vaccine, knowing in September it was 50 percent, so September, October, November, the 1st of December, we could have had a modified drug, even if it is limited supply, that we could have tried—whether it is an antigen or a new vaccine entirely, wouldn't you have recommended let us try this and do trials, see what the result is, did we solve it, can we do this in 12 weeks and the next time? So my question: Did you do it? Did you try to do anything to modify the vaccine that was wrong?

Dr. SCHUCHAT. Um-hum. I want to stress that we were not——

Mr. MCKINLEY. It is a yes or no, isn't it?

Dr. SCHUCHAT. There were many activities taken to address the emergence of drifted strain, including preparing a candidate vaccine virus——

Mr. MCKINLEY. Did you try and modify it?

Dr. SCHUCHAT. The issue of protection is both what strains are dominant, what efficacy the vaccine has, and how many people can

get the vaccine. So a highly effective vaccine with very few doses available may not be as good as a moderate- or a low-efficacy vaccine and a lot of doses available.

Mr. MCKINLEY. I will take your answer——

Dr. SCHUCHAT. I don't think that——

Mr. MCKINLEY [continuing]. As a no, that you didn't try and——

Dr. SCHUCHAT. No, what I am saying is that we did begin to prepare the candidate vaccine virus so that companies would be able to produce a vaccine against the drifted strain. This particular strain has been quite challenging to produce vaccines against.

Mr. MCKINLEY. Thank you. Fifty thousand Americans died.

Mr. MURPHY. Now recognize Ms. Castor for 5 minutes.

Ms. CASTOR. Thank you very much.

Dr. Schuchat, on average, maybe take the last 10 or 20 years, how many Americans suffer each year from influenza, how many are hospitalized, and how many die?

Dr. SCHUCHAT. Thank you. Yes, for the past 5 years or so, we have ranged between 19 and 35 million cases of influenza illness each year, between 110,000 and almost 600,000 hospitalizations each year, and 5,300 to 39,000 deaths attributable to influenza. Those are in the past 5 years. In that same period, the vaccination efforts we have had have been reducing the full burden by about 16 to 17 percent. You know, we would have more disease, deaths, and hospitalizations without vaccination, but it is not as high a prevented——

Ms. CASTOR. Um-hum.

Dr. SCHUCHAT [continuing]. Fraction as we see for measles, where we are preventing 99 percent, you know, of the disease. And that is partly because we don't have high coverage.

Ms. CASTOR. How many are vaccinated?

Dr. SCHUCHAT. Well, we have gone from 19 percent of Americans getting vaccinated against flu, to 46 percent. So that is a big improvement, but it is not the majority yet. The other factor though besides the coverage is the effectiveness, and even in a good year, we are seeing vaccines that work about 60 percent efficacy, and so that is why we are very committed to the interagency work on developing vaccines that could have higher effectiveness, particularly in the most vulnerable populations.

Ms. CASTOR. And when it comes to the deaths, what age range? We know the elderly are more vulnerable, but what are the——

Dr. SCHUCHAT. Yes, you know, the vast majority of deaths are in seniors, but unfortunately, we do have children die every year. More than 60 children have died so far this flu season, and I fear that is not going to be the end of it. So we know that statistics say if you are elderly, if you have medical immunocompromising conditions, if you are under 2, you have more chance of being hospitalized or dying from flu, but many parents can tell you that their child was perfectly healthy and they actually lost a child. So I really want parents and the general public to know to take flu seriously.

Ms. CASTOR. And this year, it is a particularly severe flu season with higher rates of hospitalization and mortality. This is especially worrisome for those vulnerable populations; children, the elderly, pregnant women, and others with weakened immune sys-

tems. Dr. Midthun, the severity of this year's flu can be partially attributed to the fact that it is an H3N2 predominant year. Tell us what that means in simple terms. The fact that this is an H3N2 predominant year. Dr. Midthun.

Dr. MIDTHUN. I think oftentimes in H3N2 prevalent years, there may be more morbidity and mortality, although I think it is very important to remember that all influenza can cause morbidity and mortality. H1N1 was responsible for 2 pandemics, 1918 and the one in 2009. And also B strains can be very serious, especially for children, and cause very serious outcomes. But Dr. Schuchat may want to add to that.

Dr. SCHUCHAT. Yes. Overall, the H3N2 serious years have higher total morbidity and mortality, but as Dr. Midthun says, the H1N1 has a predilection for younger people.

Ms. CASTOR. Uh-huh. So you were talking about the effectiveness of the current vaccine before this year's flu vaccine shows 23 percent effectiveness. I want to hear more about how we assess the flu vaccine effectiveness, and better understand this. How do we gather information on infections and mortality and then test for vaccine effectiveness?

Dr. SCHUCHAT. One of the things that the investments in influenza have permitted, the resources that CDC has gotten over the past several years, is expansion of the systems by which we track influenza, and track influenza vaccine coverage, and track influenza vaccine effectiveness. So we have much better data today than we had several years ago. We are able to provide estimates in the middle of the year of how many people have gotten vaccinated, as well as how well the vaccine is working so far.

We work with State and local health departments in the surveillance systems, and we work with academic university partners in measurement of influenza vaccine effectiveness, essentially, comparing people who have influenza laboratory-confirmed disease with others to look back at their vaccination history and basically quantify the vaccine effectiveness that way. We release our data every week on something called FluView. It is on our Web site. And so you can essentially look in October 3 and see the first information about the drifted strain. So every week as that comes out, you can follow what is going on. But in mid-January, in fact, we sped up the vaccine effectiveness estimates so that the public would know them as quickly as possible.

Ms. CASTOR. Well, I know I marched my whole office down to get the flu vaccine, but I think this is very important that people understand what the experts are saying today, that this mismatch, parents with children need to be especially careful because of the predilection for younger folks. But in America, if we only have 46 percent, and that is kind of high watermark for flu vaccinations, we can do a whole lot better. So thank you very much.

Mr. MURPHY. Thank you.

And now I recognize Dr. Burgess for 5 minutes.

Mr. BURGESS. Thank you, Mr. Chairman.

And, Dr. Schuchat, let me just pick up for a moment on what you were discussing with the vice chair of the subcommittee, Mr. McKinley. Now, you had a drifted strain that kind of appeared on the scene. The Southern Hemisphere designation is out of phase

with what the vaccine release in the Northern Hemisphere, correct? So you had identified the drifted strain when the recommendation was made for the inclusion in the vaccine that was released in the Southern Hemisphere, is that correct?

Dr. SCHUCHAT. Yes, that is right.

Mr. BURGESS. So why not then come forward with a recommendation for a booster shot or some additional protection for people in the Northern Hemisphere if we already were developing a different vaccine based on a drifted strain for the Southern Hemisphere? Your neighbors to the north might have been interested in that, don't you think?

Dr. SCHUCHAT. You know, the manufacturing capacity to respond in September to vaccine strain recommendations in large number of doses would get us a large number of doses probably February or so. So I mean Dr. Robinson might be able to comment a little bit more, but the ability for us to make a Northern Hemisphere recommendation for a vaccine in September, and have doses in time for the flu season, would be very low. And we take that type of step when we are worried about a pandemic, and I think the committee is raising the question of should we take that type of step when it is not a pandemic situation but a drift.

Mr. BURGESS. We would like you to react with a little bit more clarity and be flexible when so many lives are on the line, as Mr. McKinley outlined. And I mean, look, we are dealing with a, what, a 40 percent uptake of the vaccine as it is. If people read the headlines and say only 1 in 5 are protected anyway, I would just as soon not get stuck.

Dr. SCHUCHAT. Yes.

Mr. BURGESS. So I would think you, as an agency, you would want to have that flexibility and want to show utility for people that we are on top of this, we are working on this 24 hours a day, 7 days a week, 12 months out of the year. We are monitoring your health and your safety when it comes to the flu virus, and we can't be perfect every time, but when we are not, we are going to be there to help you stave off the effects. I mean, again, that is what I am hearing as a result of this hearing. And as Dr. Fauci acknowledged, we have had these hearings before. We had a hearing when we only had a trivalent vaccine, and we talked about a quadrivalent vaccine. I mean these things, they are important, people do pay attention to them. Our vaccine rates for influenza are lower than they should be for the country.

Dr. SCHUCHAT. Um-hum.

Mr. BURGESS. I have gotten my flu shot every year except 2004 when it was politically inadvisable for a Member of Congress to receive a flu shot because there was a shortage——

Dr. SCHUCHAT. Right.

Mr. BURGESS [continuing]. Because of the serratia contamination that occurred in one of the manufacturing labs. Separate story, but every other year I step up and get the vaccine because I meet a lot of people every day, I ride on an airplane twice a week, this is just a commonsense reaction to what is an inevitability on the ground.

I want to shift gears for just a moment, and I do feel obligated to talk about the measles issue because it has achieved so much

in the way of headlines, and I am going to breach—I am going to violate HIPAA, and I just want to tell HHS that I am going to violate HIPAA. I am going to release sensitive clinical information about myself. So I never had the measles vaccine. I didn't have it because I was too old. I mean I was—well, when I was a child in the '50's, it hadn't—it wasn't there, it wasn't available. I don't remember every scraped knee, every sniffle from my childhood, but I remember the measles.

Dr. SCHUCHAT. Um-hum.

Mr. BURGESS. It was bad. I mean you can see—and I see in Harrison's here online, hard, shaking chills. I mean that—it—yes, hard, shaking chills doesn't even begin to describe it. The chills are so hard they are painful. You want to cover up, you want to pull a blanket around yourself, but you don't want anything touching your skin. That is measles. I mean it is a different disease. And we had forgotten about it, quite frankly, because, you know, you just never see it, and now we are faced with the prospect that we are seeing it. It is important for parents to have their children vaccinated.

Dr. SCHUCHAT. Um-hum.

Mr. BURGESS. There are things that can happen to you as a consequence of having had the measles. I remember in medical school learning about subacute sclerosing panencephalitis, and I remember asking at the time why do I have to learn about this, no one is going to get it anymore. But, in fact, people may get it because it is a consequence of having had an infection with measles. So these issues are important.

Now, if I recall correctly, and suddenly somehow this is interjected into presidential politics, which is inappropriate because, if I recall correctly, since President Gerald Ford, there has not been a Federal mandate for any vaccination. And I will ask that question generally to the panel, Dr. Fauci, am I correct on that?

VOICE. Microphone.

Dr. FAUCI. When President Ford essentially mandated through the department that there be massive vaccination for the 1976 influenza, that famous catastrophic event with the Guillain-Barre, but I don't think there has been official mandating about——

Mr. BURGESS. Correct. So these are State-mandated vaccines that people have to take before attending public schools, and there is a reason for that. It should be a State mandate. There is no one asking for a Federal mandate. It doesn't mean that the vaccination is not important. And for people who are listening and paying attention today, please have your children vaccinated.

Thanks, Mr. Chairman. I will yield back.

Mr. MURPHY. Thank you.

I now recognize Mr. Green for 5 minutes.

Mr. GREEN. Thank you, Mr. Chairman. Thank our panel for being here.

Data from the National Immunization Survey found that fewer than half of children and adults are vaccinated by November of this current flu season. My numbers said 40.3 percent, but, doctor, you said 46 percent. Forty-six percent of the people and 6 months or older received the flu vaccine. These numbers seem similar to what we have seen in the last few years.

I wanted to hear why these vaccination rates continue to be so low and what we can do to improve it, although I have to admit, the recent news that it is only 20 percent—23 percent effective, and those of us who are much older it may only be 12 percent, that would probably tell people not to get it. But somehow along the way, we need to do it, and encourage much more than 46 percent to be able to get that. The data showed that nearly 60 percent of the people had not taken advantage of it. Is that accurate?

Dr. SCHUCHAT. The 46 percent that are vaccinated is based on last year's end of season, so the 40-some percent was the early, you know, by November, how many had gotten vaccinated.

You are right that the majority still haven't gotten the flu vaccine, and this is something that we think is going to take years of work. Part of the issue is whether there is a concern about the disease, and part of the issue is whether there is confidence in the intervention. And as you know, the intervention has different efficacy, different years. So it is not a simple message and it is one that we work hard to communicate honestly and clearly.

Mr. GREEN. Well, I guess part of the problem is if we think it is bad now with the news coverage about the less effectiveness, what can we do to make sure that next year we have, one, an effective flu vaccine—I know it is almost like throwing darts against the wall—and that way we will convince more people to get it, because, again, the more people vaccinated, the more we will defeat it.

Dr. SCHUCHAT. The vaccine prediction is most of the time good. So out of the last 20 years, this is the fourth time where there has been an important mismatch. And in some of the previous times where there has been mismatch, there has still been much higher efficacy than what we are seeing this year. This year will be a difficult year to follow in terms of our messaging. We do want people to know that influenza can be serious, and that the vaccine is still the most effective way to reduce your risk, but we also want people to know about antivirals, because we think those are also underutilized and could actually reduce the duration of the illness, and even reduce the chance of being hospitalized in some patients. And so we think it is important to get both messages out.

Mr. GREEN. Is there anything that Congress could do because, when you found out that the effectiveness was so low—I know there were some questions earlier from Dr. Burgess saying, OK, we need a booster for those of us who got the vaccine—are there resources available where you could do that and make it an issue, saying, you know, it is only 23 percent but this booster will get you to 50 percent?

Dr. SCHUCHAT. You know, I think the resources that have been provided have been incredibly valuable, and there is both a short-term and a long-term strategy. You know, the short-term strategy, to use available tools better, and to make incremental improvements in the production and distribution of vaccine, and the long-term strategy that Dr. Fauci and Dr. Robinson were talking about with the research and investments in universal vaccines. So I think we can't just do one or the other, we really have to do both, but it will be years before there is that really much, much, much better flu vaccine. And we are fortunate that we have a lot of options now and a much better supply horizon than we have had, you know, 5

or 10 years ago. So I think we really need to just stick with it and make those incremental improvements, and make sure that the public gets the correct information, the accurate information, that we are honest when he have a year like this where it is quite difficult. And unfortunately, the vaccine is only preventing about 23 percent of what it might be, but that is still significant protection.

Mr. GREEN. Well—and again, since the percentage is lower for the most vulnerable population of the elderly, we need to encourage the elderly to—even if it is only, I don't know what percentage it was, 12 percent, because it still gives them that 12 percent. But we would sure like to see it up above the efficiency much better.

Dr. SCHUCHAT. Yes. Ironically, the elderly are the best at getting vaccinated. It is about 70 percent or so of them, but the vaccine works the worst in that population. And they really do rely on the rest of the population being protected to have more confidence that they will be safe too. So it is one of those vaccine-preventable diseases where the more people that are immunized, the better. And, of course, in the future we hope that we will have even more effective tools.

Mr. GREEN. I know this has come up before, but——

Mr. MURPHY. Thank you.

Mr. GREEN [continuing]. Ranking Members Pallone and DeGette yesterday talked about the measles outbreak in Disneyland, and I know that is a concern too that—to do it. And let me just follow up, Mr. Chairman, I remember when I was in the fifth grade, the whole county, we got a polio vaccine. Was that mandated by the Federal Government?

Dr. SCHUCHAT. You know, in that era, you didn't need to mandate polio vaccines. People were lining up. I think the whole country was so thrilled that there was a polio vaccine licensed——

Mr. GREEN. Um-hum.

Dr. SCHUCHAT [continuing]. In 1955 because that was such an incredible scourge. The mandates, the school requirements, really were shown in the 1980's to massively reduce the risk of measles outbreaks in schools, and it was really only when States required kindergarten entry to have measles vaccine documentation that we started to get a better handle on——

Mr. GREEN. Thank you.

Dr. SCHUCHAT [continuing]. Measles, and then——

Mr. GREEN. Yes.

Dr. SCHUCHAT [continuing]. Of course, in 2000, we were able to eliminate native measles here in the U.S.

Mr. MURPHY. The gentleman's time has expired. Thank you.

I now recognize Mr. Griffith of Virginia for 5 minutes.

Mr. GRIFFITH. Thank you, Mr. Chairman.

Let me try to get some blanks filled in here. I don't have the answers. The meeting took place with WHO in CDC and FDA and others in February. In March, we know that there was a drift that was picked up of about 10 percent, is that correct?

Dr. SCHUCHAT. Actually, it was lower than that.

Mr. GRIFFITH. About 7 percent I think I saw in your testimony.

Dr. SCHUCHAT. It was like 4 percent.

Mr. GRIFFITH. OK. Do we know what April was, because we have a few numbers on the chart but we have a lot of question marks? And if you don't——

Dr. SCHUCHAT. In April——

Mr. GRIFFITH [continuing]. You can provide it——

Dr. SCHUCHAT [continuing]. Fourteen viruses were shown that had reduced susceptibility to the strain, and that was out of 127, so that would be 11 percent.

Mr. GRIFFITH. OK. And then we have a number from May. Then June and July, we don't have another number on this chart until September. What were you all seeing in June, July and August?

Dr. SCHUCHAT. In June, July, and August, there were 88 viruses identified from the whole world that had reduced reaction, and so that comes to 36 percent.

Mr. GRIFFITH. OK.

Dr. SCHUCHAT. With reduced, you know, that were mismatch.

Mr. GRIFFITH. And then there is another meeting, and there is a different Southern Hemisphere recommendation made, and we don't make the—I think that is five. If you can get us the other numbers just so we can kind of track it, that would be great. But then——

Dr. SCHUCHAT. Absolutely.

Mr. GRIFFITH [continuing]. My question comes up, and I am happy for anybody to answer it, why didn't we have the manufacturing capacity for the virus to do turn somewhere in this process, I think you said by June, July, we were in the 36 percent range, recognizing that flu season doesn't generally hit in a big way for another fair number of months, why does the United States lack that manufacturing capacity, and as a subpart of that, if there was the capability of producing, and I am trying to pronounce this correctly, monovalent vaccine, why didn't we do so? And if you all could focus on that. Any member of the panel please.

Dr. SCHUCHAT. Yes, maybe I can start and let Dr. Robinson continue.

I think one thing to recognize in the summer is that we were looking at increasing proportions of H3N2 that were not well matched to the vaccine, but we still had the other 2 or 3 different strains that were in the vaccine. So the concept of producing a monovalent vaccine—we might have been asking the American public to take a monovalent vaccine plus the tri or quadrivalent seasonal vaccine. As we have been hearing, the American public isn't all that keen to get one flu vaccine a year. Would they really be lining up to get 2? But there are, of course, major limitations in the manufacturing capacity to make 2 different products for the same season. So I will let Dr. Robinson answer that.

Mr. GRIFFITH. Dr. Robinson?

Dr. ROBINSON. Thank you. During the manufacturing season, they are producing three or four vaccine strains all the way to June, maybe even July if it is a tough year for them. At that time—and most of those are egg-based. At that time, they within the summer are putting those together, we call them blending and putting together, to go forward with the vaccine that was released in September to go out on the shelves.

The ability to have what was called a competent vaccine that could be very quickly—that is certainly true, it can be maybe faster than some of the egg-based vaccines, but the capacity that we have right now with the licensed vaccine, the only one recombinant-based vaccine, is very, very small. It would have only been able to produce maybe hundreds of thousands of——

Mr. GRIFFITH. OK. Let me——

Dr. ROBINSON [continuing]. Doses.

Mr. GRIFFITH. Let me ask the why on that. Is it because there is not a profit——

Dr. ROBINSON. No, no.

Mr. GRIFFITH [continuing]. To be made?

Dr. ROBINSON. One instance, it is a new vaccine——

Mr. GRIFFITH. OK.

Dr. ROBINSON [continuing]. And, two, since it is a new vaccine, they are just scaling up to the market. This is an incumbent market, very competitive, and they were licensed in 2013. We are actually supporting their efforts in building a much larger facility to produce maybe tens of millions of doses, and so that they actually can going forward be able to produce, say, 50 million doses in 4 months of a monovalent vaccine for a pandemic or, maybe in this case, another influenza vaccine.

Mr. GRIFFITH. So you anticipate that our capacity will be greater in the next couple of years than it is today to react?

Dr. ROBINSON. Indeed, it will be, because we will actually have the cell-based influenza vaccine facility down in North Carolina that has a large capacity, and we will be able to have that product on the market. But again, they are limited in that they are making seasonal flu vaccine at the same time that we may have wanted to do that.

The other thing is that these manufacturers also produce vaccines for the Southern Hemisphere. So when they came off of making the vaccine for the Northern Hemisphere, then they started back to actually making the vaccine for the Southern Hemisphere. So we would have had to make a decision and tell them in September, stop doing that and go forward with the new vaccine. And we know that that is a difficult midcourse shift.

Mr. GRIFFITH. But if we——

Dr. ROBINSON. The future will be——

Mr. GRIFFITH. But we could have done that even in, say, July when we knew we were at 36 percent that had drifted?

Dr. ROBINSON. It would have been very, very difficult, sir.

Mr. GRIFFITH. OK. All right. I appreciate it. I see my time is up and yield back.

Mr. MURPHY. All right, I want to clarify something. So you said 36 percent, June, July, and we have a 50 percent cutoff. So some time in September the 50 percent number was significant enough to say, OK, we need to do something different in the Southern Hemisphere. What is the magic number where you say we need to make a change here?

Dr. SCHUCHAT. Actually, it wasn't that there was something different, it is that every September the strains are reviewed worldwide. All——

Mr. MURPHY. Why not——

Dr. SCHUCHAT [continuing]. Of them.

Mr. MURPHY. Why not August? What I am concerned about is, we want to break through, if there is some bureaucratic hurdles, this committee wants to help——

Dr. SCHUCHAT. Thank—yes.

Mr. MURPHY [continuing]. But if you say, well, we don't look at this until—we don't really meet and discuss this until September, that is not a lot of solace for what Mr. McKinley was raising for the hundreds of thousands of seniors who are going to be sick. What—what is—what do we do?

Dr. SCHUCHAT. Right. In September every year, the groups convene to review all the data for the Southern Hemisphere production, and that is because it takes that long to get vaccine that will be ready by that time. It is not——

Mr. MURPHY. I am not——

Dr. SCHUCHAT [continuing]. Because we are not looking all the way between.

Mr. MURPHY. Yes, but you have already said you can get a vaccine ready in 12 weeks when you need a monovalent strain when there was a pandemic.

Dr. SCHUCHAT. Not——

Mr. MURPHY. Wasn't that done in 2009, you did something quickly——

Dr. SCHUCHAT. No.

Mr. MURPHY [continuing]. Dr. Robinson?

Dr. ROBINSON. OK, go ahead.

Dr. MIDTHUN. No——

Mr. MURPHY. I want to be clear.

Dr. MIDTHUN [continuing]. I think in 2009 the virus emerged in April. In May it was recognized that it was causing significant disease, and at that time a decision was made across the HHS that a monovalent vaccine would be pursued. And so all stops were pulled out to do that, but in point of fact, the first vaccine was not available from—for that H1N1 monovalent until the end of October, and the bulk of vaccine was not available until late December, into January. So just point taken that the manufacturing process itself takes many months, and although we——

Mr. MURPHY. To get to the critical number. I know it is Mr. Tonko's turn, but we are talking about just to start to give it to some seniors and high-risk group.

Mr. Tonko, you are recognized for 5 minutes.

Mr. TONKO. Thank you, Mr. Chair. And welcome to the panel.

There has been much discussion here today about parents and the advice they get about having their children vaccinated or not vaccinated. I would like to ask it from yet another perspective. Yesterday, a United States senator asserted that routine vaccinations could cause, and I will quote, "walking-talking normal children to wind up with profound mental disorders."

And so my request of the panel is a simple yes-or-no response. Is there any shred of credible evidence that shows that this, in fact, is the case? Dr. Schuchat?

Dr. SCHUCHAT. Not the vaccines we are using today.

Mr. TONKO. Dr. Midthun?

Dr. MIDTHUN. No, not for the vaccines we are using today, although I think it is important to note that any vaccine can have some safety issues associated with it, but typically, they are very rare, and that is why we also have the Vaccine Injury Compensation Program.

Mr. TONKO. Dr. Robinson?

Dr. ROBINSON. I am in agreement with Dr. Schuchat and Dr. Midthun.

Mr. TONKO. Dr. Fauci?

Dr. FAUCI. Agree.

Mr. TONKO. Pardon me?

Dr. FAUCI. Agree with my colleagues.

Mr. TONKO. Thank you for clarifying.

In addition to promoting vaccination, Dr. Schuchat, how else does the CDC work to prevent spread of the flu? For example, does the CDC recommend symptomatic individuals to stay home from work?

Dr. SCHUCHAT. Yes, we have a multipronged approach to prevention. The best protection is to get vaccinated. We also recommend sensible measures like washing your hands, covering your cough, staying home when you are sick, staying away from other people when you are sick. And then, of course, if you are ill, and particularly those with underlying conditions or the elderly, we think prompt antivirals can be important, and so talk to your clinician about that.

Mr. TONKO. Are there any data showing how many flu transmissions occur in the workplace when symptomatic individuals do come to work?

Dr. SCHUCHAT. I don't have that data, but there have been analyses showing the value of vaccination to reduce workplace absenteeism and to improve productivity.

Mr. TONKO. Um-hum.

Dr. SCHUCHAT. So we think it is a good thing for health, and it is also a good thing for the workplace to be protected against flu. To stay home for when you are sick for a variety of conditions is good counsel.

Mr. TONKO. I do know that in speaking with my constituents, there are a number of working moms and dads who can't afford to take time off of work because it would mean they are not paid, and so they attempt to come to work even though they really shouldn't. In your opinion, would paid leave policies help to prevent the transmission of the flu and other illnesses by encouraging more workers to stay home when they are indeed sick?

Dr. SCHUCHAT. We think the easier it is for people to do the right thing, the better.

Mr. TONKO. OK, thank you.

Dr. Midthun, the FDA has licensed a number of new vaccines since the year 2009. How have these new vaccines contributed to preparedness efforts in the last several years?

Dr. MIDTHUN. Thank you for that question. I think what they have done, especially with regard to the cell-culture-based vaccine and the recombinant protein vaccine, is they offer an alternative manufacturing platform relative to the egg-based manufacturing that was the basis for the vaccines that had been approved up until that time. And it is always important to have a diversified way in

which you can manufacture vaccines. It also widens the platform available in the event of a pandemic because, typically, the pandemic vaccines are made on the same manufacturing platforms that the seasonal vaccines are made on, and so it really provides greater diversity and more resilience.

Mr. TONKO. And, doctor, in your testimony you talked about work to speed up the manufacturing process for existing vaccines. Can you tell us more about that work?

Dr. MIDTHUN. Yes. It is actually a very strong collaboration between BARDA, CDC, NIH, and ourselves, and it looks at a number of different aspects. One aspect is to look at the potency testing that is done for vaccines. Right now, that relies on reagents that are made by immunizing sheep, you develop antiserum, this usually is a process that can take up to 2 months. And so, obviously, having potency assays that are much more rapid would really decrease the time that it takes to do this, to make these reagents. And so there are some approaches using more modern platforms, and in conjunction with some of our colleagues, there actually are some tests that are being planned that will be embarked upon later this year to compare some of these newer assays to the standard assay that is used right now, the radial immunodiffusion test, to see how these compare to each other in actual testing of vaccine samples that the manufacturers are providing to us. And some of the manufacturers have actually expressed interest in also participating in the testing to see what the feasibility is. So that is one aspect that we are working on.

Another one that has been very important, and that the CDC and others have really done a lot of work on, but we have also contributed to, is to try to identify high-growth viruses that will lead to good yield when you grow the virus in the eggs or in the cell culture. As you recall, Dr. Fauci was referring to the fact that that can often be a rate-limiting step. And so trying to develop viruses that you know will yield high growth when these new strains emerge could really facilitate and take time off that process.

And then also there was the sterility testing, and the FDA actually changed its regulations in 2012 to allow for more flexibility in sterility testing. Up until that time, it was very prescriptive and this 14-day test by USP had to be used, but now manufacturers can come in with novel testing, and we actually know that some, you know, testing that has been described in the literature could actually be accomplished in 5, 6 days potentially.

Mr. TONKO. Thank you.

Mr. MURPHY. Thank you.

Mr. TONKO. I yield back, Mr. Chairman.

Mr. MURPHY. Thank you.

I now recognize a new member of the subcommittee, Dr. Bucshon, who is a cardiothoracic surgeon by training, and is here from Indiana. Welcome to the subcommittee, and you are recognized for 5 minutes.

Mr. BUCSHON. Thank you, Mr. Chairman. First of all, I would like to associate myself with the unanimous comments of our expert panel in recommending that parents get their children immunized to prevent childhood diseases. All my children are immunized.

Based on the testimony we have heard today, it seems like we could have had a monovalent vaccine available by maybe December, and if that is true, Dr. Schuchat, do you lack the authority to make that happen in that way, because through the testimony, I think a lot of members have asked what can we do to help, but for us, for Congress, to help, we have to have a specific thing to help with. So is there new authority or any other authority that would be helpful to make this happen?

Dr. SCHUCHAT. I don't believe so. The key issues is a risk assessment and trying to predict the most likely course of events, but I believe there are authorities if the decision is made to go ahead with the monovalent, whether for pandemic or for drift.

Mr. BUCSHON. OK. As a healthcare provider, I know that, you know, liability is a significant issue in our American healthcare system, and not only physician malpractice, but product liability is a substantial issue, I know, that has an effect on the healthcare industry. Anyone can comment on this. Do product liability issues affect our ability to act in a more nimble way when it comes to vaccines, because you do have private companies that produce these. And so let us start with that and then I will spearhead off from there.

Dr. SCHUCHAT. The Vaccine Injury Compensation Program exists so that product liability won't be a factor, so that we can make sure that we have vaccines made but the people who are injured by vaccines are compensated. And so the funding from that comes from an excised tax on every vaccine dose that is sold, so that we know that vaccines are very safe, but there are sometimes rare, important complications, and the Injury Compensation Program exists for those families who have been injured.

Mr. BUCSHON. OK. Thanks for clarifying that, and I think that is important to understand.

Dr. Midthun, from the FDA's standpoint, is there—how do I want to say this—a risk-averse regulatory process? It seems like at the FDA, you know, over a number of years—but for a variety of reasons have—I think been, in my view, sometimes overly cautious with new products or changing quickly. Do you see that as an issue, you know, and that comes into the liability issue again, is there resistance or reluctance to quickly move based on the concern about these type of things?

Dr. MIDTHUN. No, I don't see that. I think in the influenza domain, we, every year, are primed to approve the new vaccine strains that are recommended for inclusion in the vaccine those years. I think also our record of having approved since 2003—I think in 2003 we had three licensed influenza vaccines. Today we have 16 licensed influenza vaccines, including our cell-based, recombinant-based, quadrivalent, high-dose, and also I should point out that many of those we actually approved using accelerated approval, which actually allows us to approve something based on the new response that is likely to predict clinical benefit. And so we have used accelerated approval regulations to approve many of those and get them to market more quickly. So I think we—and also I should point out we approved the novel adjuvanted H5N1 vaccine in 2013. So I think that we really looked very carefully,

and balanced the benefits and the risks, and are really very flexible.

Mr. BUCSHON. Great. That is good to hear.

There is a recent CDC study that looked at clinician practices on patients that come to the emergency room with—and the data is striking, only 16 percent of patients with laboratory-confirmed influenza were prescribed antiviral drugs.

So the first question I have, do they work? Do the antiviral drugs work?

Dr. SCHUCHAT. Yes, last week there was a new meta-analysis of all the published and unpublished randomized control trial data on Oseltamivir, and it shed new light on the benefits as well as potential risks that—there is——

Mr. BUCSHON. So they——

Dr. SCHUCHAT [continuing]. Benefit for the work.

Mr. BUCSHON. Short answer, they do work, because I am running out of time.

Dr. SCHUCHAT. Yes.

Mr. BUCSHON. Because surprisingly, 30 percent of the patients with laboratory-confirmed influenza were—30 percent were prescribed one of three common antibiotics, which are for bacteria, not viruses. Is there anything that we can do to better, you know, as a physician, better make the, you know, change that practice? Maybe Dr. Fauci can answer that.

Dr. FAUCI. Yes, that is another whole issue of antimicrobial resistance, which we have even discussed before this committee. So certainly, over the last year, there has been an extraordinary effort on the part of the Congress and the administration in everything from executive orders to 5-year plans to counter the kinds of practices that lead to antimicrobial resistance, and one of the most common, as I am sure you are aware, sir, is that someone comes in with a viral infection and they get an antibiotic. That is very, very common, unfortunately.

Mr. BUCSHON. I yield back, Mr. Chairman.

Mr. MURPHY. Thank you.

I now recognize a new member to the committee, Ms. Yvette Clarke, who represents—Ms. Schakowsky is next? I am sorry, I thought Clarke was next.

Ms. SCHAKOWSKY. I was here earlier.

Mr. MURPHY. All right, thank you.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman.

So if the vaccine that we are using now has been viewed as 23 percent effective, and usually in the past it has been 50 to 60 percent effectiveness, are we seeing—maybe it is Dr. Schuchat, are we seeing a commensurate increase in the incidents of flu?

Dr. SCHUCHAT. Yes. When we compare this season with 2 years ago, the 2012/13 season, the last big H3N2 season, much of the pattern is similar, but our hospitalizations in the elderly are much higher at the same time this year. So we will get the end-of-season statistics, but it has been a very bad year for the elderly.

Ms. SCHAKOWSKY. I see. So the lab tests predicted 23 percent——

Dr. SCHUCHAT. Um-hum.

Ms. SCHAKOWSKY [continuing]. But you are seeing it actually out in the country, that it is also much higher?

Dr. SCHUCHAT. Right. Yes, we are seeing, you know, both the lab mismatch and then our vaccine effectiveness low estimate, and then the incidents of the hospitalizations is high.

Ms. SCHAKOWSKY. OK. With the passage of the Affordable Care Act in 2010, we took important steps on preventive medical coverage for free, and since the law went into effect, approximately 76 million Americans have received no-cost coverage for preventive services. So I am wondering if we are seeing that there actually was an impediment to getting these preventive services, vaccines, because of the cost, and now without the cost, that more people are making that available to themselves.

Dr. SCHUCHAT. For influenza vaccine, I think it is too soon for us to see, but we do know that there are important disparities in influenza vaccination coverage, and that insured people have been more likely to be vaccinated than uninsured. So I think that over the years ahead, we may start to see some progress there.

Ms. SCHAKOWSKY. So we do think, although we don't have the new data——

Dr. SCHUCHAT. Um-hum.

Ms. SCHAKOWSKY [continuing]. That cost has been a barrier in the past——

Dr. SCHUCHAT. That is right. We——

Ms. SCHAKOWSKY [continuing]. Is that what you think?

Dr. SCHUCHAT. And we know even for the workplace, for instance, when workplaces will offer flu vaccine for free for workers or, particularly for healthcare workers, the uptake is better than when it is out-of-pocket, off-site, need-to-seek vaccine.

Ms. SCHAKOWSKY. I think it is great that we are having this hearing today because this whole question of vaccines, as many of my colleagues have mentioned, has really been in the news, and it is disturbing that a number of high-profile political figures have weighed in on this in a negative way, I would say, that this is, you know, parents should make the decision, and I have seen some children that have been deeply affected by vaccines in a negative way. What I am wondering is, what is the public health outreach effort to make sure that—you heard my colleague Marsha Blackburn talking about the mom blogs. I mean there is a lot that is going on, not only on television, and I am glad you were on, Dr. Fauci, and that is very important that we get the message out in every medium, but I am just wondering if we are also just looking at how people are communicating with each other in the social media and getting the facts out.

Dr. SCHUCHAT. Yes, we spend quite a bit of time and attention monitoring the social media as well as the general media, and we work closely at the national level, but also at the State and local level, on communication, both direct to consumer as well as through clinicians and other trusted partners, because we think getting information that speaks to you close to where you are is really important in your health behaviors.

I would just like to say that the vast majority of parents vaccinate their kids against most of the recommended diseases on time, and yet there are some minor voices that get a lot of attention.

Ms. SCHAKOWSKY. Exactly. I think maybe we need to make sure we communicate with all political voices as well that are out there to make sure that we are communicating the science, the facts, that suggest that all parents should vaccinate their children.

So I yield back.

Mr. MURPHY. All right, now we recognize Mr. Flores from Texas, who is also new to this committee. Third term in Congress, and we welcome him to this subcommittee.

Mr. FLORES. Thank you, Mr. Chairman. I also want to thank the panel, particularly for your positive comments regarding the benefits of having children vaccinated for measles. I have an extended family member who has not done that for her children yet, and it just baffles me why she can't do that. And so I hope she is hearing this today, that she heard your comments, and that she will do so.

I want to talk about the weakness in the strain selection process, and talk about the opportunities to mitigate that weakness. And I want to focus my questions to you, Dr. Robinson, because BARDA is a tool, I think, that we have to do this.

And so my first question is this. Is BARDA funding any projects or initiatives to develop two things: one, better testing technologies, or two, better approaches for making the vaccine candidates?

Dr. ROBINSON. So the answer is yes on both. In my testimony, I identified that we were supporting the development of evolutionary biology methods that would actually help the existing methods inform what strains are out there. There are only so many ways a virus can mutate.

Mr. FLORES. Right.

Dr. ROBINSON. And we know that you can do the experiments to show which ones would predominate, and that may actually inform which ones we may see the next season. And certainly, the underpinning of that the NIH has funded over the years, and so we are moving forward primarily for our pandemic purposes, but certainly could be used in seasonal. So that is one way towards the selection, and then informing new vaccine designs.

Mr. FLORES. OK.

Dr. ROBINSON. Secondly, with the technologies, we have supported with our colleagues here from NIH, CDC, and FDA, new technologies to make these vaccines, whether it be cell-based or recombinant. And working with the NIH, we are looking at universal flu vaccine candidates with a number which Dr. Fauci enumerated of going forward. It is not because those technologies haven't been tried before, but as he explained, there is a limitation in how the body actually sees these viral proteins. And so there are some new ways now that we can do that, we couldn't do before.

Mr. FLORES. And in terms of looking at BARDA's priorities, where would you say that getting these better technologies for the strain selection process is in your sort of list of all the things you have to do on your wish list?

Dr. ROBINSON. Yes. Well——

Mr. FLORES. Is it in the top third, or the middle, or the bottom, or——

Dr. ROBINSON. No, it is at the top.

Mr. FLORES. OK.

Dr. ROBINSON. Yes.

Mr. FLORES. Great. Sounds like we should keep it there, from what I am hearing today.

The third question is how can we expedite the development and deployment of better technologies, say, use of genetic sequencing, to detect virus change, which you have talked about, to ensure that the U.S. has a vaccine that can be matched to a drifted H3N2 strain?

Dr. ROBINSON. Certainly, one of the ways that we actually have employed with biosynthetic technology work with the Craig Venter Institute and then one of the manufacturers. We did that in 2013 with H7N9 to actually come up—what we didn't need the traditional way of having the virus actually sent from one laboratory to another. We actually had the nucleotide sequences available, then using that, and actually made the virus seed strains and went forward with H7N9. Regardless of if it is an egg-based or cell-based or recombinant, we can do that.

Mr. FLORES. OK.

Dr. ROBINSON. And we are moving forward with those efforts also.

I just want to say one other thing that Dr. Midthun had talked about, and that is high production yield seed strains. Why is that important? It means that the virus doesn't have to be passaged to eggs or cells or medium many times because, very early on, we can actually have high production seed strains, and that is why the manufacturers keep passaging the virus to get high production. If we had that immediately, then the virus that actually is in the vaccine is going to be very similar to the circulating virus.

Mr. FLORES. Um-hum.

Dr. ROBINSON. Much more so.

Mr. FLORES. OK. And then the last question I have: I have always been fascinated with the initiatives to try to develop the universal flu vaccine, and I appreciate what Dr. Fauci talked about today, and educating the committee and subcommittee on how to do that.

What role does BARDA play in the development, deployment and stockpiling of a universal flu vaccine?

Dr. ROBINSON. So certainly hand in hand with the NIH, we are moving forward with the development, not only for seasonal, as I had pointed out, for pandemic purposes. It may serve as a primer for future pandemic vaccines. Again, you may only need one dose of the pandemic vaccine as opposed to two which you normally would need. And so we can stockpile that vaccine or actually have it as part of our commercial products that are out there every year.

Mr. FLORES. OK. Thank you for your responses. As you know, this is important to me because you have a facility in my district that I think is doing some great work.

Mr. Chairman, I yield back.

Mr. MURPHY. Thank you.

And now I recognize Ms. Clarke of New York, the Brooklyn area, as a new member of the subcommittee. Welcome. You are recognized for 5 minutes.

Ms. CLARKE. Thank you very much, Mr. Chairman.

Being the low one on the totem pole, oftentimes, it comes with the territory.

Let me welcome our panelists as well, and pick up on some of the line of questioning that my colleague Mr. Tonko raised with respect to research.

So, Dr. Fauci, your testimony discussed the potential for a universal flu vaccine that could provide protection against numerous strains of the flu over several seasons. What can you tell us about the research on this vaccine?

Dr. FAUCI. OK. So the research on this vaccine, as I had mentioned, really starts off with the fundamental basic observation that a part of the protein that is the target of the vaccines that we have developed over decades is one that, unfortunately, has a component of it that tends to change from season to season. We refer to that as a drift. Big change is the shift. The part that doesn't change is the part that we have just recently recognized on the thin stem part of the protein that we now know that if you show it to the immune system in a certain way, and you can only do that by molecular biological techniques because, generally, when you show the immune system the whole virus, the part that you really wanted to make an immune response is crowded out and covered by the larger part. So now you are essentially teasing it out and showing the immune system just the part that you want to make a response again. And we have done that. We have done it with a number of different platforms, and we have shown now in a small animal, in a ferret, and now even in a human, that, A, it is feasible, B, it is safe, and C, it does induce the kind of response that you would predict would have a much broader effect.

So that is the real first solid step. We have to perfect that, and then we have to show in a broad study that it actually does protect against multiple strains.

Ms. CLARKE. That sounds very promising, Dr. Fauci.

Dr. Robinson, you mentioned in your testimony a new initiative to support development of new flu vaccine candidates that offer broader, longer-lasting immunity. Can you tell us more about this initiative?

Dr. ROBINSON. Certainly. We are working with Dr. Fauci with many of the candidates that he has talked about, and in addition, there are other ways in which we can broaden the immunity. Some might be with adjuvants, and other designs of the vaccines going forward, and not only for seasonal but for pandemic purposes.

Ms. CLARKE. So it sounds like we are moving into the 21st century.

Dr. ROBINSON. Yes.

Ms. CLARKE. Very well. Very well. I would like to shift a bit to the idea of strains, the strain selection process, Dr. Midthun. Can you outline the role of the FDA's Vaccines and Related Biological Products Advisory Committee in the strain selection process, and when does this process actually begin?

Dr. MIDTHUN. The process is actually year-round. CDC and other WHO collaborating centers for influenza are monitoring influenza strains year-round to be looking for trends, changes, emerging situations, so that is going on all the time. Then you have——

Ms. CLARKE. How does the advisory committee arrive at its recommendations on the selection of a strain?

Dr. MIDTHUN. OK. So what happens in usually February or early March, when the Vaccines Advisory Committee meets, is that we have experts come and present the data on the influenza strains that have been circulating over really the last year, and those strains are evaluated to see which appear to be prevalent, and really based on those data a decision is made about which vaccine strains should be included in the vaccine manufacturing. And then once that recommendation is made, of course, the manufacturers then use that information to start manufacturing their vaccines. But I think a very important point to note is that, typically, manufacturers actually start manufacturing the vaccine before the advisory committee is even held. They usually start in January. Why? Because they are aware of the data also. As I mentioned, this is an ongoing process year-round, and so they will usually anticipate what they think will be the strain that is not going to change. They do this at risk, but the point is that——

Ms. CLARKE. That is what I was going to ask——

Dr. MIDTHUN [continuing]. It is a process——

Ms. CLARKE [continuing]. Has there ever been an incident where perhaps the advisory committee did not necessarily agree and the manufacturer is already proceeding?

Dr. MIDTHUN. Yes, that can happen. I mean you would have to ask individual manufacturers——

Ms. CLARKE. Yes.

Dr. MIDTHUN [continuing]. But I suspect that that has definitely happened, although, typically, I think they will go with something that they think, based on the data, is unlikely to change. But it really is a process where we make the recommendation in February, but clearly, there is a lot of work that precedes that and there is a lot of work that continues after that to actually have vaccine available. And usually vaccine becomes available in July, August, that time frame, and then it is continued to be released really throughout the end of October. So you can see it is a process that, even though you do a recommendation in February, and much work starts before that even, it really does take many, many months to actually have vaccine available for the influenza season——

Mr. MURPHY. Thank you.

Dr. MIDTHUN [continuing]. Which, you know, typically can begin, you know, October, November, although sometimes not until later.

Mr. MURPHY. Thank you.

Ms. CLARKE. Thank you.

Mr. MURPHY. Thank you.

Now I recognize another new member for the committee, Susan Brooks of Indiana, who has a second term of Congress. Previously she was in the Homeland Security Committee and was a U.S. Attorney. We look forward to you being a part of this committee. You are recognized for 5 minutes.

Mrs. BROOKS. Thank you, Mr. Chairman. I do want to thank all of the witnesses for your work with respect to the public health and safety of our citizens. On Homeland Security, I chaired the subcommittee on emergency preparedness response and communications, and this is something that we know everyone is passionate about. I think, obviously, when we have an epidemic the way we

have right now, the public pays a lot more attention to it, but I think the public also expects us to get it right. And the public is expecting us to leave no stone unturned and to continue to ask the questions and figure out how can we do it better, how can we do it faster, what mistakes have we learned from in the past, and what do we do to keep our country safe.

This year is a much higher death toll, as you have said. In Indiana, there were 72 deaths statewide. The year before, 70. We have already had 108 deaths in Indiana, and it is just the end of January, and the flu season, as I understand it, goes often in through May, so we have a lot that we are very, very concerned about. I spoke with the head of our Marion County, which is Indianapolis' Public Health Department, and she has indicated that the flu has gotten so severe in Indianapolis that she is barring anyone under the age of 18 from visiting hospitals. So if you are 15 years old and your mom is in the hospital, you can't visit your mom. So we have reached, just to let you know, as I am sure you know, and you are very focused on this, but these types of precautions are obviously being taken for the safety of the patients, but we also know, as we have heard, vulnerable, you know, whether they are children or seniors, are so vulnerable. But yet one of the things she also shared with me, and she was explaining the ag. culture technology that we use, and it takes a long time, but yet she shared the new cell mediated technology that you have mentioned in production is faster, but yet it is not widely used. And so I would like to explore why.

You mentioned a cell-based facility in North Carolina. Can we please talk a bit more about if these technologies are out there, why are they not being more widely used? And I don't know if, Dr. Schuchat, you want to start, and Dr. Robinson.

Dr. SCHUCHAT. Yes, I will just make an overview comment that production of flu vaccine has been increasing over the past decade, with more, you know, factories in the U.S., more companies, more products, but we also have to work on demand, and the more vaccine we use every year, the more the companies will make. They don't make lots of vaccine at a risk. And so it is a cycle that is interdependent. But Dr. Robinson can talk about the cell-based plant and some of the other manufacturing efforts.

Mrs. BROOKS. And is that correct, that a cell-based technology would allow vaccines to be produced faster? Is that correct or is that not correct?

Dr. FAUCI. Not significantly faster. The cell-based is more consistent, whereas eggs, you know, it depends on supply of eggs, whereas you can keep growing up cells. I think that is a common misconception that there is a game-changing difference in the amount of time it takes. And the answer to that, and I am sure Robin will verify that, isn't the case. You both have to grow the virus, that is the problem, as opposed to in a recombinant DNA or molecular technology, be able to make it more quickly. So even though we welcomed the transition, and hope we even do more from egg to cell, the answer for the time frame itself is not going to be solved by cell-based technology.

Mrs. BROOKS. What is the answer to shorten the time of production?

Dr. FAUCI. And that is what I just said when I was talking about changing from a need to grow the virus, to the ability to do it from a molecular way where you actually develop a vaccine by recombinant DNA technology, which doesn't require your having to grow the virus. That is really the major transformation from one platform to another.

Mrs. BROOKS. Dr. Robinson, how do we——

Dr. ROBINSON. No, I agree with them. I mean that is where we see the biggest savings in time is with recombinant vaccines, but they are new and they are just with very limited capacity, they will grow in time. With the cell-based vaccines, we may even be able to shave a couple of weeks off than what we have with the standard egg-based vaccines at this time.

The other issue is that it is a new product, and this is a very competitive industry, and they are trying to get their market share at this time. And as they improve to be equal to or better, then they will actually become more commonplace in the overall vaccine supply.

Mrs. BROOKS. So are you saying that there is just one manufacturer that is manufacturing in that manner?

Dr. ROBINSON. That is cell-based in the U.S., there is only one licensed manufacturer.

Mrs. BROOKS. Is there any issue in the licensing process?

Dr. MIDTHUN. No, there is no issue in the licensing process. We have approved one cell-based manufacturer and one recombinant-based manufacturer. We basically work with anyone who wants to come in and make a product, and we are there to facilitate that process, but it really is up to, you know, the sponsor to come in and say we would like to do this. Certainly, you know, BARDA has done much to support some of these new technologies, and certainly, again, we are grateful for the support you have given in that regard.

Mrs. BROOKS. OK.

Mr. MURPHY. Thank you.

Mrs. BROOKS. Thank you.

Mr. MURPHY. We now recognize another new member of the committee, Markwayne Mullin of Oklahoma. We welcome you, and you are recognized for 5 minutes.

Mr. MULLIN. Thank you, Mr. Chairman.

Dr. Robinson, my State of Oklahoma has been hit particularly hard this year. According to Walgreens, Oklahoma City is the number one place for prescriptions to be issued out for Tamiflu. Tulsa is number five. I think we have had somewhere like 50 deaths, and in the neighborhood of 1,300 individuals being hospitalized. My family was hit real hard this year. Out of my five kids, four got it. My fourth daughter, who is 6, received actually two different strains of the flu. My wife and all my family missed the swearing in because of the flu. And now it is kind of ironic that I am sitting up here talking about this.

Just some follow-up questions. My understanding is, part of the challenge of being able to respond to the mismatch vaccine is the burden of regulations, but underneath declaration of maybe an emergency, those regulatory burdens change. Is that correct?

Dr. ROBINSON. Certainly, if a public health emergency is declared then we can move forward, but there are regulatory issues, I think Dr. Midthun may want to testify——

Mr. MULLIN. No, I just wanted a yes or no on it. If it is declared an emergency, those regulatory burdens change quite a bit, right? OK.

In 2009, the President declared a public emergency during the swine flu, or the H1N1, crisis. That is correct, right?

Dr. ROBINSON. Correct.

Mr. MULLIN. How many cases of swine flu had been confirmed, not deaths but had been confirmed in the U.S., when the President declared that public emergency?

Dr. ROBINSON. I think Dr. Schuchat can answer that.

Dr. SCHUCHAT. I don't have the numbers, but there was a——

Mr. MULLIN. It was 20.

Dr. SCHUCHAT [continuing]. An enormous change in the epidemiology——

Mr. MULLIN. We do have the number, there were 20 of them that was in that——

Dr. SCHUCHAT. Well, but instead of flu coming down, it was going up after the season——

Mr. MULLIN. Right.

Dr. SCHUCHAT [continuing]. With a completely different strain.

Mr. MULLIN. But there was——

Dr. SCHUCHAT. So——

Mr. MULLIN. But there was an emergency declared with only 20 confirmed cases in the U.S. There has already been 50 deaths in just my State of Oklahoma.

Dr. SCHUCHAT. Um-hum.

Mr. MULLIN. So I am trying to make a comparison here.

I believe the flu season goes through May in the Northern Hemisphere, is that correct? Right?

Dr. SCHUCHAT. It can extend to May. It can end earlier.

Mr. MULLIN. OK, what exactly is the definition of a public health emergency? Dr. Robinson, do you want to take that? What are the criteria of us meeting a public emergency?

Dr. SCHUCHAT. Yes, a public health emergency is not a black-and-white definition.

Mr. MULLIN. So there is no set of specific criteria that we can look at, like the number of deaths or hospitalization to determine what is in the public's best interest as far as a health emergency?

Dr. SCHUCHAT. Yes, the issue with a pandemic is that the potential impact is exceptionally greater than the normal range. It——

Mr. MULLIN. So it doesn't matter how many deaths we have, it is just 100 percent of——

Dr. SCHUCHAT. One would be——

Mr. MULLIN [continuing]. CDC to make that——

Dr. SCHUCHAT. One would be declaring that much in advance of seeing the deaths, because of the time needed to take steps to intervene.

Mr. MULLIN. Would it help if Congress or you guys could come up with maybe some criteria that we could look at that could maybe trigger it, rather than just waiting for the next crisis to happen, or, honestly, a public outcry?

Dr. SCHUCHAT. I think we could probably provide the language about a public health emergency. What I was trying to say was that it is not the same for each condition, for each disease or——

Mr. MULLIN. I understand there is some type of flexibility and, you know, there has got to be a little bit of more understanding of what we are dealing with, but it seems odd that there is no criteria at all for us to understand it——

Dr. SCHUCHAT. Yes, I——

Mr. MULLIN [continuing]. When something like the swine flu, that just had 20 cases in the country, was declared an emergency by the President, and yet we have a pandemic going on right now with the flu, and we could have maybe changed some of this with the regulatory burdens going through if we would have declared it an emergency faster, where maybe we could have got help to individuals.

Dr. SCHUCHAT. In 2009, a new strain emerged from animals that had genetic re-assortment that was completely unique to humans. And so what we are dealing with with the drift is slight changes, a very different scenario. But what you indicate is correct that the ultimate burden of disease from a drifted H3N2 strain may end up being greater than a completely new to humans re-assortment like the H1N1——

Mr. MULLIN. So——

Dr. SCHUCHAT [continuing]. Swine-origin pathogen in 2009.

Mr. MULLIN. Could you maybe help us maybe draw some type of criteria that needs to be laid out so the next time this happens, we could have something to compare it to?

Dr. SCHUCHAT. We would be happy to provide follow-up on the public health emergency and how that is defined. Sure.

Mr. MULLIN. Thank you. I yield back.

Mr. MURPHY. Thank you. Gentleman yields back.

I now recognize another new member of our committee and subcommittee, Chris Collins of New York, a second term in Congress. Welcome aboard, and you are recognized for 5 minutes.

Mr. COLLINS. Thank you, Mr. Chairman.

I will be as quick as I can to get the information really directed more at Dr. Fauci and Dr. Schuchat.

And I appreciate your issue of the jump on swine flu, the same thing we were worried about with the bird flu, that didn't happen. That is the good news of RNA viruses, they don't jump off to—but if they do, it can be devastating. So my question is really on the universal vaccine discussion. And I don't think it has been made clear here. We have DNA viruses and we have RNA viruses. And when we talked about the vaccine for HPV, the vaccine for herpes, smallpox, chickenpox, those are all DNA vaccines. And it is relatively straightforward to get a vaccine for a DNA-based virus. Then you have your RNA viruses; HIV, Ebola, West Nile, SARS, influenza. They mutate a lot, that is what they do, but they don't jump species much.

So my question is this: Since we are talking about an RNA virus, so you can't compare influenza with HPV, you can't compare influenza with herpes, and I don't think that was made clear, but now that we are talking about an RNA-based virus, I guess my question is this, because they mutate, drift so often, that is the insidious na-

ture of RNA viruses, which is why the answer to a lot of the questions coming here is more because they do mutate, that is the basis of that virus. So how is it that since measles is an RNA virus, polio is an RNA virus, rubella is an RNA virus, and so is mumps, so you have mumps, measles, rubella, and polio on the one hand, RNA, and we have vaccines for them, what is the difference in the reason we don't have vaccines for things like influenza?

Dr. FAUCI. You have asked a very complicated question, and I can tell you that there is not a one-to-one relationship of whether you can or cannot get a vaccine, whether it is an RNA or a DNA vaccine. And also, RNA viruses do jump species. I mean the——

Mr. COLLINS. Rarely.

Dr. FAUCI. Yes—well, HIV, influenza, I mean, there is the fowl virus that jumps, HIV, the chimp virus that jumps, so——

Mr. COLLINS. Yes, but much less——

Dr. FAUCI. Yes.

Mr. COLLINS [continuing]. Likely than a DNA virus.

Dr. FAUCI. But the things that go into whether or not—your point is very well taken, that if you have in general, and——

Mr. COLLINS. Um-hum.

Dr. FAUCI [continuing]. You have to be really careful when you pick this one or the other one, in general, a virus that has a proofreading mechanism, which RNA viruses have——

Mr. COLLINS. Right.

Dr. FAUCI [continuing]. They don't correct their mistakes when they mutate, allows it to do what influenza does——

Mr. COLLINS. Right. Right.

Dr. FAUCI [continuing]. Drift. It allows it to do what HIV does. If you give it one drug, it will mutate to be resistant unless you give it——

Mr. COLLINS. Sure.

Dr. FAUCI [continuing]. Three drugs.

Mr. COLLINS. Sure.

Dr. FAUCI. You are perfectly correct on that. However, it really isn't specifically that. These are easy to make one against, and these are difficult. It just doesn't work that way because there are a lot of other things that go into whether or not you are going to have a successful vaccine. But the fundamental principles that you mentioned are correct.

Mr. COLLINS. So how did we end up with one for measles, polio, and why has it been so god-awful, if not impossible, to get one for HIV or influenza? Is there any——

Dr. FAUCI. Well, the body makes a very good immune response against measles, even when it is a serious disease. Ultimately, the body will completely clear measles in the——

Mr. COLLINS. Right.

Dr. FAUCI [continuing]. Overwhelming majority of people. So we already know the body has the capability of inducing an effective immune response, therefore, you follow what the body does and you induce the same response that natural infection does. With HIV, the body does not make an adequate immune response against HIV, so there is no proof of——

Mr. COLLINS. Yes, but now, HIV, that is where the immune system doesn't even see the viral particles.

Dr. FAUCI. Well——

Mr. COLLINS. Now, that is different than influenza.

Dr. FAUCI. Well, I am sorry, sir, it does see it, it just doesn't make a good response.

Mr. COLLINS. It doesn't react to it.

Dr. FAUCI. It doesn't make a good response——

Mr. COLLINS. Right.

Dr. FAUCI [continuing]. Against it.

Mr. COLLINS. Right, but that is what is unique about HIV.

Dr. FAUCI. Exactly. You need the body's ability to do it naturally to mimic it. That is what vaccines are all about; mimicking natural infection without——

Mr. COLLINS. Sure.

Dr. FAUCI [continuing]. Hurting the host.

Mr. COLLINS. So one real quick question for Dr. Schuchat. They use adjuvant-based vaccines in Europe. We don't do it here. The question on the monocrobial, if we did that with an adjuvant, we could extend that production, we could produce much less, extend it, because you were saying production is the big issue. If it was adjuvant-based, you wouldn't need as much. Should we be looking at that as a natural part of the monocrobial?

Dr. SCHUCHAT. You know, I think that adjuvanted influenza vaccines hold a lot of promise, and I know that the FDA has licensed one so far in the U.S. In terms of extending the supply and also——

Mr. COLLINS. Right.

Dr. SCHUCHAT [continuing]. And also potentially expanding the immune response. As you heard from some of the measles discussions, here in the U.S. our population has a lot of questions about vaccines and about their safety, and they have, even in 2009 when we were doing community engagement around H1N1 vaccination, we had lots of questions about whether there would be adjuvants in those vaccines or not. In Europe, they use adjuvanted——

Mr. COLLINS. Right.

Dr. SCHUCHAT [continuing]. H1N1 vaccines and we didn't. Our public really needs to come along with us in the scientific endeavor, and so I think that is an area where the FDA is really critical in reviewing the safety data.

Mr. COLLINS. Yes. Thank you very much.

Yield back, Mr. Chairman.

Mr. MURPHY. Thank you, Mr. Collins.

And now as a tradition of this committee, if another member of the committee wishes to be part of this, we will welcome back a former member of the subcommittee for this special visit, Mrs. Ellmers of North Carolina. You are recognized for 5 minutes.

Mrs. ELLMERS. Thank you, Mr. Chairman, and thank you to our ranking member also, for allowing me to be part of this important subcommittee hearing on this very timely issue. And to our panel, thank you for being here today.

And I just want to point out a couple of things. One, in October, looking at this issue and knowing the importance of it moving forward, especially when it comes to vaccine production, I had the honor of hosting a roundtable discussion in the Research Triangle. Dr. Midthun and Dr. Robinson, thank you again for participating

in that very important discussion. We learned a lot from that. As we all know, Chairman Upton is leading the 21st Century Cures Initiative, and the vaccine space fits right in there. And I am working on very important legislation right now to actually bolster vaccine production and bring vaccines to market. As we know, it is very, very important. And I have also the honor of having the facility in Holly Springs, North Carolina, which has been referred to already, which will be addressing the issue of seasonal and pandemic vaccine production, using the cell culture technology. Very important to my district. And I also want to point out, and I think this is something that we need to look at into the future when we are trying to solve these problems. This was a public-private partnership between Novartis, HHS, and BARDA. So, again, thank you all for your input today. This is a very, very difficult situation, but I believe that we can get ahead of it and we can move forward, and we can identify ways that we can improve upon this process.

Dr. Schuchat, I have a question for you. In the legislation that I am working on right now, my bill, we create mechanisms to help increase the communication and sharing between the CDC and industry, and ways that we can get that information out to impact public health. In your opinion, how can the CDC work more closely in partnership with industry to reduce the risk and uncertainty of investing in the novel vaccines?

Dr. SCHUCHAT. We appreciate the chance to work closely with industry as they are doing their early development and research.

Mrs. ELLMERS. Um-hum.

Dr. SCHUCHAT. We welcome companies to come meet with us to share their ideas, and we——

Mrs. ELLMERS. Um-hum.

Dr. SCHUCHAT [continuing]. Share all of the information——

Mrs. ELLMERS. Um-hum.

Dr. SCHUCHAT [continuing]. We have in terms of the public health burden——

Mrs. ELLMERS. Um-hum.

Dr. SCHUCHAT [continuing]. Need and likely interest in terms of public or providers.

Mrs. ELLMERS. Um-hum.

Dr. SCHUCHAT. So we do that regularly, and we welcome the opportunity to do it systematically.

Mrs. ELLMERS. Dr. Midthun, again, thank you for being here, and again, thank you for being a participant in the roundtable discussion that I had back in the District in October. As we are looking at vaccine manufacturers to more readily export vaccines from the U.S. and make them available to people around the world, again, the legislation that we are working on right now helps to expedite the licensure process. In addition to expediting export licenses, what else can the FDA do to help speed up production and approval on delivery of flu vaccine availability?

Dr. MIDTHUN. No, I think we currently use all the expedited pathways that are available. So we can use accelerated approval, which we——

Mrs. ELLMERS. Um-hum.

Dr. MIDTHUN [continuing]. Have done for numerous influenza vaccines.

Mrs. ELLMERS. Um-hum.

Dr. MIDTHUN. We also did recently for the 2 meningococcal B vaccines that we approved; one in October and one just last month. We also used the breakthrough designation which basically means that there is a very concerted interactive approach early on and throughout the process with industry to really accelerate the development of products. So we use all of these tools, and they are very important. They, of course, do rely on having certain science.

Mrs. ELLMERS. Um-hum.

Dr. MIDTHUN. So, for example, to use——

Mrs. ELLMERS. Sure.

Dr. MIDTHUN [continuing]. Accelerated approval, you typically rely on what we call a surrogate endpoint. Usually in the case of a vaccine it would be some immune response. But you need to have information that actually indicates that this immune response is——

Mrs. ELLMERS. Um-hum.

Dr. MIDTHUN [continuing]. Is really likely to predict clinical benefits. So there is also a scientific piece that is very, very important that others, for example——

Mrs. ELLMERS. Um-hum.

Dr. MIDTHUN [continuing]. In industry, NIH, and other partners, need to work on——

Mrs. ELLMERS. Um-hum.

Dr. MIDTHUN [continuing]. To make that kind of——

Mrs. ELLMERS. Um-hum.

Dr. MIDTHUN [continuing]. Process available, but we work very closely, obviously, with our sponsors to facilitate whatever their development plans are.

Mrs. ELLMERS. Thank you. And one last comment that I would like to make, Mr. Chairman, if you would indulge me. One of the concerns that was raised by Mr. Tonko from New York, having to do with the issues that our families are dealing with, with sick children and having to take time off of work, I would advocate for my good friend, Martha Roby from Alabama, she has a wonderful bill, Working Families Flexibility Act, that actually addresses this issue and allows our workforce to be able to take part in the availability and ability to use overtime and bank it so that in the event that pediatric appointments need to be made, or any of these things, families can make those choices. So I would advocate to the co-sponsorship of that bill. It is a very good bill, and it addresses the very issues that we are talking about today.

Mr. MURPHY. Thank you.

Mrs. ELLMERS. So thank you, Mr. Chairman, and I——

Mr. MURPHY. Thank you.

Mrs. ELLMERS [continuing]. Yield back.

Mr. MURPHY. And I want to thank the panelists. Look, I think we are all frustrated, we need to be speeding up this process and the science, and if there are other legislative things we need to do, please let us know. This is the day after Groundhog Day, and I don't want to be here with another Groundhog Day a couple of years from now running into the same problems, with the same issues, and having the same crisis with so many Americans getting sick and dying for whatever this is. So I ask——

Ms. DEGETTE. Would the gentleman yield for one second?

Mr. MURPHY. Yes.

Ms. DEGETTE. I completely agree with the Chairman, but I will say I want to commend this panel and others at the CDC and NIH because, having been on this committee now for 18 years, we really have made advances from when we first started with those early hearings on egg-based technologies. We just need to accelerate that. So anything we can do to help, we are here to help. Thank you.

Mr. MURPHY. Appreciate that. I ask unanimous consent that Members' written opening statements be introduced into the record, and without objection, the documents will be entered in the record.

In conclusion, thank you again to the witnesses and Members that participated in today's hearing. I remind Members they have 10 business days to submit questions for the record, and I ask that all witnesses agree to respond promptly to those questions.

And with that, this committee is adjourned. Thank you.

[Whereupon, at 12:34 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

THE COMMITTEE ON ENERGY AND COMMERCE

MEMORANDUM

February 1, 2015

TO: Members, Subcommittee on Oversight and Investigations

FROM: Committee Majority Staff

RE: Hearing on "Examining the U.S. Public Health Response to Seasonal Influenza"

The Subcommittee on Oversight and Investigations will hold a hearing on Tuesday, February 3, 2015, at 10:00 p.m. in 2123 Rayburn House Office Building, entitled "Examining the U.S. Public Health Response to Seasonal Influenza." This hearing will focus on the role of U.S. public health agencies in protecting the U.S. population from the spread of seasonal influenza. The Subcommittee will examine the strain selection decision-making process, how U.S. public health agencies are improving the effectiveness of response to seasonal flu, and the progress of Federal efforts into developing a universal flu vaccine, advanced diagnostics, new flu vaccine manufacturing technologies, and new anti-viral drugs for treatment of influenza.

I. WITNESSES

- Dr. Anne Schuchat, Director, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC);
- Dr. Karen Midthun, Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA);
- Dr. Robin Robinson, Director, Biomedical Advanced Research and Development Authority (BARDA), Office of the Assistant Secretary for Preparedness and Response; and,
- Dr. Anthony Fauci, Director, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH).

II. BACKGROUND

A. About Seasonal Influenza

Influenza is a contagious respiratory illness caused by varying virus strains and can range in severity from mild to lethal. In both its seasonal and pandemic forms, influenza is an ongoing

public health concern. In the northern hemisphere, seasonal influenza may begin as early as August and generally diminishes by April. An average of 62 million Americans – about 20 percent of the U.S. population – get the flu each year.

Influenza is considered one of the leading causes of death in the U.S., especially in a severe season. Based on 2010 data, CDC has posted the following listing: [1]

Number of deaths for leading causes of death:

- Heart disease: 596,577
- Cancer: 576,691
- Chronic lower respiratory diseases: 142,943
- Stroke (cerebrovascular diseases): 128,932
- Accidents (unintentional injuries): 126,438
- Alzheimer's disease: 84,974
- Diabetes: 73,831
- **Influenza and Pneumonia: 53,826**
- Nephritis, nephrotic syndrome, and nephrosis: 45,591
- Intentional self-harm (suicide): 39,518

(Bolded to add emphasis).

According to CDC estimates for the 1976-2006 time period, seasonal influenza has been associated with as few as 3,000 and up to almost 50,000 deaths each year in the U.S. On average each year, more than 36,000 individuals die and more than 200,000 are hospitalized from influenza and related complications.[2] A study published in 2007 estimated that more than $10 billion is spent annually in direct medical costs for hospitalizations and outpatient visits from seasonal influenza-related complications.[3]

Detailed published estimates of influenza-attributable deaths by age, type, and subtype have not been updated by the CDC for seasons beyond the 2006-2007 influenza season.[4] CDC does not know exactly how many people die from seasonal flu each year. The reasons for this include: States are not required to report individual seasonal flu cases or deaths of people older than 18 years of age to CDC; many influenza-related deaths, such as from pneumonia, may not include any mention of influenza on the death certificate; many patients (especially the elderly) may die from pneumonia unrelated to influenza, so figuring out which cases to include in an analysis can be difficult; most people who die from seasonal flu-related complications are not tested for flu or they seek medical care when flu can no longer be detected.

---

[1] CDC FastStats, Death and Mortality, *available at* http://www.cdc.gov/nchs/fastats/deaths.htm.

[2] In a January 28, 2015 phone briefing with staff, the Acting Director of the CDC's Influenza Division stated the estimates for hospitalizations could be as high as 400,000.

[3] CDC Congressional Justification FY 2015, *available at* http://www.cdc.gov/fmo/topic/Budget%20Information/appropriations_budget_form_pdf/FY2015_CJ_CDC_FINAL.pdf.

[4] Gonçalo Matias, Robert Taylor, François Haguinet, Cynthia Schuck-Paim, Roger Lustig and Vivek Shinde, "Estimates of mortality attributable to influenza and RSV in the United States during 1997–2009 by influenza type or subtype, age, cause of death, and risk status," Influenza Journal 507 (June 27, 2014), *available at* http://onlinelibrary.wiley.com/doi/10.1111/irv.12258/full. However, CDC has indicated to staff that there is an update that covers the 2005-2014 period that will be released shortly.

Given the difficulties on getting the exact number of flu-related deaths, researchers have turned to a variety of modeling techniques to estimate deaths. One retrospective database analysis, which estimated influenza deaths in the U.S. by analyzing data for 12 influenza seasons (1997-2009), found that influenza deaths were highest in older and high-risk individuals. In terms of deaths from influenza and pneumonia, CDC statistics[5] show that, between 1999 and 2011, there were on average some 20 deaths each year (high of 23 and low of 17) per 100,000 of the U.S. population.

Other recent data and CDC statements indicate there is no reason to think that there has been any major change between 2011 and 2014. Over the 1999-2011 period, the death rate per 100,000 was 35 for the group aged 65-74; 140 for the group aged 75-84, and 600 for the 85+ group. There was also a higher than average death rate for infants of less than one year. Adults between 20 and 50 obviously had much lower rates. The figures do not distinguish between those who had received a vaccine shot in a particular year and those who had not; nor any who had a history of previous flu shots.

When the influenza (H3N2) viruses are predominant, they tend to cause more severe illness and hospitalization among the elderly. According to one study, the H3N2 A strain accounted for a seasonal average of 71 percent influenza-attributable deaths compared to the other strains.[6]

The primary method for preventing influenza is an annual vaccination. CDC recommends annual vaccinations for everyone aged 6 months or older. For the 2011-2012 season, about 42 percent of Americans aged 6 months and over were vaccinated.[7] Data from the 2012-2013 season showed that 45 percent of Americans 6 months or older got vaccinated.[8] For 2013-2014 season, the overall vaccination rate was 46 percent.[9] The estimate for this season as of November 2014 was 46.2 percent. According to the CDC fiscal year (FY) 2015 Congressional Justification, the CDC set a performance measure for the long term objective to increase the proportion of adults (18 and older) who are vaccinated annually against influenza. In FY 2013, the CDC set the target at 42 percent, but that target was not met. The FY 2014 target was 50 percent, and the goal for FY 2015 was 53 percent.

HHS has set a goal for States to vaccinate 70 percent of their population as part of the Healthy People 2020 initiative. According to experts, vaccination rates need to be generally above 70 percent for "herd immunity" effects – which limit the spread and protect those without

---

[5] www.cdc.gov/nchs/faststats/deaths.htm
[6] Matias, *supra*, note 4.
[7] Written testimony of Dr. Thomas Frieden, CDC Director, before the House Energy and Commerce Subcommittee on Oversight and Investigations, February 13, 2013 at 8 (indicating that the rate was 52 percent but that was for the subgroup of Americans aged 6 months to 17).
[8] Flu Vaccination Coverage, United States, 2012-13 Influenza Season, http://www.cdc.gov/flu/fluvaxview/coverage-1213estimates.htm.
[9] 2010-11 through 2013-14 State, Regional, and National Vaccination Trend Report, http://www.cdc.gov/flu/fluvaxview/reports/reporti1314/trends/index.htm.

immunity – to become apparent. If all seniors received a newly available high-dose version of the flu shot, flu cases among this high-risk population could drop 25 percent.[10]

B. Developing the Seasonal Influenza Vaccine

Because circulating influenza virus strains change, a new vaccine is produced and administered each year to protect against strains expected to be most prevalent that year. As FDA noted in testimony before the Subcommittee on Oversight and Investigations in 2013:

> Influenza is a very challenging virus in that its surface proteins change constantly to evade both our immune systems and vaccines. As a result of these changes, in most years, at least one of the strains in the vaccine must be changed to keep up with changes in the circulating virus.[11]

Each year, public health experts, including those from FDA, the World Health Organization (WHO), and CDC study influenza virus samples and global disease patterns to identify virus strains likely to cause the most illness during the upcoming season. Based on that information and the recommendations of FDA's Vaccines and Related Biological Products Advisory Committee (VRBAC), FDA selects the strains for inclusion in the annual influenza virus – two strains of influenza type A and one strain of influenza type B – to include in the annual influenza vaccine.[12] Because of the lead time needed for manufacturing flu vaccine, the decisions on strain selection need to be made usually by the end of February for the vaccine to be available for the next flu season in the U.S.

There are about 150 million doses of flu vaccine available annually in the U.S., with about 140 million doses from egg-based manufacturing and 10 million doses from cell- and recombinant-based. The estimated lead times to first dose for each type of manufacturing are as follows: egg-based, 22-24 weeks; cell-based, 16-17 weeks; and recombinant, 12-15 weeks.

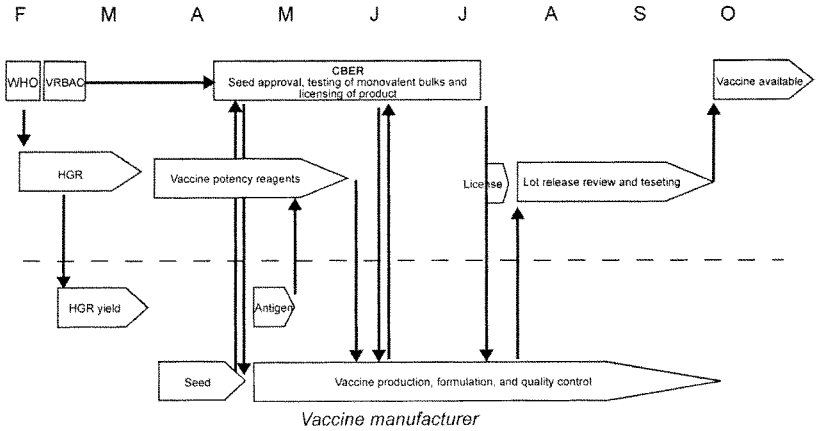
---

[10] R. Roos, "Large trials finds high-dose flu shot beneficial for seniors," CIDRAP, August 13, 2014, http://www.cidrap.umn.edu/news-perspective/2014/08/large-trial-finds-high-dose-flu-shot-beneficial-seniors.

[11] Statement of Jesse Goodman, M.D., MPH, Chief Scientist, FDA, Hearing before the House Energy and Commerce Subcommittee on Oversight and Investigations, "Influenza: Perspective on Current Season and Update on Preparedness, February 13, 2013.

[12] This is the trivalent vaccine. Since 2013, there has also been a quadrivalent vaccine available that includes an additional B strain.

Below is a graphic illustration[13] of the annual timeline for the U.S. vaccine production process.



C. The 2014-2015 Seasonal Influenza Vaccine

CDC is reporting that flu activity remains high in the U.S. and is widespread in 46 states, D.C., and Guam. Flu activity is likely to continue nationally for several weeks. A key reason that the U.S. is experiencing a severe flu season is because this year's vaccine does not protect well against the dominant strain of influenza, which mutated after the vaccine-production process began for the 2014-15 and does not match well with the H3N2 A strain in the vaccine. Given the lead time needed for manufacturing and regulatory compliance, there was not enough time to modify the vaccine and restart the manufacturing.

Seasonal flu vaccination typically has an effectiveness[14] rate in the range of 50-60 percent.[15] Seasonal flu vaccine effectiveness studies show a low effectiveness rate of 10 percent

[13] Slide 8 from Novartis briefing to Members of the Subcommittee, January 27, 2015 (on file with Committee). HGR refers to high-growth reassortants. The viruses that are made by WHO (in eggs) as the foundation for the year's vaccine. They have surface proteins of the recommended flu strain, but the viral core of strains that are easy to grow.

[14] By effectiveness, CDC means the rate at which the vaccine prevents a person from going to the doctor to seek treatment. Thus, in a population of 100 unvaccinated people exposed to the flu virus, the CDC would expect about 10 to seek treatment. In a population of 100 vaccinated people exposed to the flu virus, the CDC would expect 4 people to seek treatment, but would prevent 6 from going to the doctor.

[15] By way of comparison, effectiveness rates for other vaccines such as for measles are about 95 percent. The comparison highlights the unique challenge posed by the constantly changing flu viruses.

(in high-risk populations) for the 2004-2005 season and a high rate of 60 percent (general population) in the 2010-2011 season. Vaccination, even with effectiveness of about 60 percent, has been shown to reduce flu-related illness, antibiotic use, time lost from work, hospitalizations, and deaths.

An interim analysis of this year's seasonal flu vaccine showed only a 23 percent rate of effectiveness for the overall U.S. population – much less so for most American adults, demonstrating only 12 percent effectiveness for those 18-49 years old and 14 percent for those 50 years or older. This is the lowest rate since CDC has collected standardized, more accurate data of effectiveness rates in the last four to five years.

The lower effectiveness is due to significant mutations in a key flu strain (the dominant H3N2 A strain) that occurred sometime after the strain selection decision for the U.S. vaccine was made in February and before the onset of this year's flu season in the U.S. This occasionally occurs. For example, CDC stated during a staff briefing that the 1999 seasonal flu vaccine had near zero effectiveness because of drift in the strain from mutations. Even with the lower effectiveness, CDC is urging influenza vaccination for any persons who have not been vaccinated yet this season, as the vaccine may still offer benefits. Antiviral drugs are a second line of defense to treat flu illness, and CDC is urging greater use of antiviral medications for the treatment of influenza.

On February 28, 2014, the FDA Advisory Committee voted to retain all 3 current strains for the 2014-2015 trivalent influenza vaccines. At the time of the February 2014 FDA recommendation, the evidence showed a 90 percent match and a 10 percent mismatch between the current H3N2 virus strain and the circulating H3N2 viruses. It is unusual to retain all current strains into another flu season. According to information on FDA's website, since 2002, only in 2003 and 2011 had the FDA Advisory Committee voted to retain all three strains. There also have been two instances, in 2003 and 2004, when the Advisory Committee deferred votes on one of the three strains.

CDC told staff that the agency first detected the drift of the H3N2 A strain in March 2014, but the drift was at an insignificant level, and not yet considered evidence of a distinctive and meaningful drift. Sometime in May, CDC found that the drift resulted in a 17 percent mismatch, representing a level of concern, but not unambiguous evidence of a significant drift.[16] CDC indicated to staff that a drift in the range of 20 to 30 percent would be considered significant, but staff did not get a clear response from CDC as to when CDC knew the drift was

[16] Whether there was enough drift seen in May 2014 to change the strain selection decision is in dispute. Dr. Andrew T. Pavia, M.D., Professor and chief of the Division of Pediatric Infectious Diseases at the University of Utah School of Medicine and who has served on federal and state advisory committees on vaccine policy and pandemic influenza preparedness, stated: "If we had picked the vaccine strain in May instead of February 2014, we would have picked the correct one. By April or May, there was good evidence of the drifted A/Switzerland strain; it wasn't clear that it was going to be the dominant strain, but there was a pretty good hint and we probably would have chosen differently." Another flu expert, Dr. Gregory A. Poland, M.D., Professor of Medicine and director of the Vaccine Research Group, Mayo Clinic said the current way of predicting the dominant virus of the coming influenza season is outdated and should be improved. L. Brookes, A. Pavia, and G. Poland, "Why Is Influenza So Difficult to Prevent and Treat? Will We See Improvement Any Time Soon?" www.medscape.com (January 23, 2015). http://www.medscape.com/viewarticle/838459_print

in this range. By September 2014, the mismatch was about 50 percent, and a vaccine candidate for the new strain was identified. As a result, the WHO recommended replacing the H3N2 A strain in the seasonal flu vaccine for the Southern hemisphere. The drift is currently at about a 65 percent mismatch level.

D. The U.S. Government's Roles Related to Seasonal Influenza

Within the Federal government, HHS has primary responsibility for coordinating the nation's response to public health emergencies, such as an influenza pandemic. HHS also is the primary department funding the research and development of influenza vaccines. Within HHS, CDC makes recommendations on who should be vaccinated, tracks the spread of influenza and vaccination rates, and disseminates public health messages encouraging vaccination and other protective measures, such as hand-washing. FDA is responsible for selecting the influenza strains to include in the annual influenza vaccines and for licensing vaccines.

1. U.S. Centers for Disease Control and Prevention

CDC had an enacted level of about $174,558,000 for influenza planning and response in FY 2014.[17]

For effective strategies for increasing flu vaccination, the CDC has advised Committee staff that there are different barriers and strategies depending on the population, but the key elements of an effective strategy are confidence in the recommendation, strong provider recommendation, and access (payment, scheduling, etc.).[18]

CDC focuses on increasing demand with healthcare providers for influenza vaccination each season through investments in health communication with providers and the general public, targeted outreach to high-risk populations, and partnerships with pharmacists as a means to extend the reach of influenza vaccination.

CDC also detects and monitors influenza through a network of laboratories at the State and international levels that are routinely testing samples to: determine the severity of the influenza season; identify viruses that are causing disease and may pose a pandemic threat; and determine the effectiveness of the influenza vaccine and other interventions.

---

[17] CDC FY 2015 Congressional Justification, 53 (CDC FY 2015 request of $187,558,000 for influenza planning and response is $15 million above the FY 2014 enacted level), *available at* http://www.cdc.gov/fmo/topic/Budget%20Information/appropriations_budget_form_pdf/FY2015_CJ_CDC_FINAL.pdf.

[18] CDC provided strategies to staff for the following groups: Health Care Personnel http://www.cdc.gov/flu/toolkit/long-term-care/strategies.htm; Adults: http://www.cdc.gov/vaccines/hcp/patient-ed/adults/for-practice/increasing-vacc-rates.html; Pregnant women: http://www2.aap.org/immunization/pediatricians/NFIDFamilyVaccinesCalltoAction.pdf.

2. U.S. National Institutes of Health & Biomedical Advanced Research and Development Authority

Below are the most current figures on influenza research.[19] NIH has not released actual figures for FY 2014 and 2015. The influenza figures include all categories of influenza research (vaccines – including universal flu vaccine research, therapeutics, diagnostics, and basic.)

NIH Influenza Funding:
- FY 2013 actual: $304 M
- FY 2014 Estimated: $312 M
- FY 2015 Estimated: $312 M

BARDA is charged with the advanced development and procurement of medical and non-pharmaceutical countermeasures for pandemic influenza preparedness and response. Thus, BARDA supports development of vaccines (including for seasonal influenza), antiviral and therapeutic agents for U.S. licensure. BARDA also supports influenza vaccine stockpiles, securing supplies of raw materials (including eggs for domestic manufacturing of seasonal and novel influenza vaccines, and the manufacturing of novel influenza vaccine candidates for clinical trials). BARDA also supports non-pharmaceutical countermeasure development, such as next-generation ventilators and procurement of masks and respirators. For FY 2014, BARDA spent about $295 million on advanced development investments and about $71 million for stockpile and infrastructure investments to support the influenza program.

3. U.S. Food and Drug Administration

In response to the Committee staff's inquiry about efforts to make improvements in strain selection decisions, FDA has pointed out global improvement efforts and the FDA's role. Improving the influenza strain-selection process and identifying scientific gaps that impact strain-selection decisions is a high priority for the WHO, regulators to improve the FDA, and vaccine manufacturers. All agree that identifying ways and approaches to improving influenza vaccine virus selection is critical. The WHO has held three meetings over the last several years (2010, 2011, and 2014), all with the explicit goal of strengthening the influenza vaccine virus selection and development process. These consultations brought together a diverse group of influenza experts, including the representatives from scores of National Influenza Centers involved in virus surveillance, representatives from the WHO Collaborating Centers for Influenza (e.g., CDC) and the four WHO Essential Regulatory Laboratories including FDA/CBER, manufacturers, and other stakeholders such as influenza modeling experts. Influenza experts from CBER participated in all three of these consultations and made presentations on variety of topics, including development of new assays and regulatory issues related to influenza vaccines. Other topics in the discussion of improvements include: expanding geographic surveillance coverage by significant increases in trained laboratory personnel and equipment; accelerating the understanding of the genetic changes in virus evolution and helping

[19] *See* Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC), http://www.report.nih.gov/categorical_spending.aspx.

predict the influence of amino acid changes on virus antigenicity from advances in high-throughput genetic sequencing; and improving assays to allow for a more accurate assessment of the quality of a protective immune response. In 2011, a WHO Conference report acknowledged an assay developed in the 1940s and still used for strain selection decisions has had performance issues in recognizing emerging changes in the H3N2 viruses.[20]

According to its Congressional justification for its FY 2015 budget request, FDA has approved 15 seasonal influenza vaccines for the United States, including Flucelvax and Flublok, two vaccines that do not use egg-based technology in their manufacturing, which offer the potential for faster start-up of the vaccine manufacturing process in the event of a pandemic. Three new quadrivalent vaccines were approved, bringing the total licensed to four that increase the likelihood of adequate protection against circulating influenza B strains. In December 2014, FDA approved Rapivab (peramivir) to treat influenza infection in adults.

In August 2010, the President's Council of Advisors on Science and Technology (PCAST) issued a report on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza. Some of the report's recommendations have pertinence to issues with seasonal flu. For example, the report recommended that the FDA should develop and issue a guidance document that defines a clear regulatory pathway for the approval of adjuvants (substances or mixtures of substances added to a vaccine to enhance the immune response) for use in human vaccines, including those for seasonal and pandemic influenza.[21] The PCAST report also recommended that FDA should develop a well-defined regulatory process for introducing alternative assays for seasonal influenza vaccines, and that FDA should define a regulatory process to guide development and implementation for sterility testing of influenza vaccines.[22]

III. ISSUES

The following issues will be examined at the hearing:

- What steps are being taken to improve the influenza vaccine virus selection?
- Could the low level of effectiveness of this season's flu vaccine been increased from 23 percent to 40-50 percent if the vaccine had been adjuvanted?[23]

---

[20] WHO Conference Report, Strengthening the influenza vaccine virus selection and development process, Outcome of the 2nd WHO Informal Consultation for Improving Influenza Vaccine Virus Selection held at the Centre International de Conferences (CICG) Geneva, Switzerland, 7 to 9 December 2011, 31 Vaccine 3209, 3213 (2013).
[21] PCAST report at 47, *available at* http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST-Influenza-Vaccinology-Report.pdf.
[22] Id. at 27.
[23] No adjuvanted influenza vaccine has ever been licensed in the U.S. to date. Dr. Andrew Pavia stated that with an adjuvanted vaccine "we probably could have made the mistake we made this year and instead of efficacy declining from 65 percent to 23 percent, it might have only declined to 40-50 percent." Brookes, et al., supra note 16.

- What actions could be taken by Federal public health agencies to help mitigate the impact of a seasonal flu vaccine that has significantly lower effectiveness?

- How can advances such as genetic characterization and rapid assessment tools improve flu surveillance and the ability to predict seasonal flu strains?

- What is the status of efforts to shorten the time and increase reliability for preparation of reagents for potency?

- Have BARDA and FDA funded applied research, as recommended by PCAST, which will develop rapid methods for assessing the concentration of antigenic materials, circumventing the need for production of new antibodies and/or traditional immunological tests?

- Has FDA developed a guidance document for developing adjuvants (a substance or mixture of substances added to a vaccine to enhance the immune response to the vaccine)? What is the importance of adjuvants in supporting the flu vaccine response?

- What is the status of the development of a universal flu vaccine?

- What is the path forward for developing a monovalent vaccine to target a significant change in a strain in the seasonal vaccine that occurs too late to modify the seasonal vaccine?

IV. STAFF CONTACTS

If you have any questions regarding the hearing, please contact Alan Slobodin, Emily Newman, or Charles Ingebretson at (202) 225-2927.

FRED UPTON, MICHIGAN
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FOURTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115
Majority (202) 225-2927
Minority (202) 225-3641

February 2, 2015

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, D.C. 20515

The Honorable Joe Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, D.C. 20515

The Honorable Tim Murphy
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Upton, Chairman Pitts, and Chairman Murphy:

We are writing to urge you to hold a hearing on the current measles outbreak and the importance of vaccinations to prevent the further spread of measles. The California-centered outbreak, which began at Disneyland in December 2014, has now led to over 100 measles cases in 14 states.[1]

Measles is an infectious disease that is prevalent in many parts of the world. Each year, approximately 20 million are infected worldwide and 122,000 people die due to the disease.[2]

---

[1] *Obama to parents doubting 'indisputable' science: 'Get your kids vaccinated'*, Washington Post (Feb. 2, 2015).

[2] Centers for Disease Control and Prevention, *Measles cases in the United States reach 20-year high* (May 29, 2014) (press release).

Measles is a highly transmissible viral disease. In the decade before the measles vaccine was introduced in the United States, more than three million individuals were infected each year.[3] It is estimated that 90% of people exposed to the disease will be infected unless they have been vaccinated. Since the introduction of the combination MMR (measles, mumps, and rubella) vaccine, there has been a 99% reduction in the number of measles cases, relative to the pre-vaccine era.[4]

In 2000, measles was declared eliminated in the United States.[5] Public health experts determined that the U.S. was able to eliminate measles because of a highly effective vaccination program and a strong public health system to detect and respond to outbreaks. However, in 2008, the U.S. experienced several outbreaks in communities with groups of unvaccinated people.[6] And 2014 saw a record number of measles cases, with 644 cases in 27 states, the highest number in the United States since 2000. CDC experts attribute these recent outbreaks to (1) more measles cases than usual in countries Americans travel to, and (2) the spreading of measles in pockets of unvaccinated individuals in the United States.

The current measles outbreak originated at Disneyland in Anaheim, California in December 2014.[7] The outbreak has spread beyond those who visited Disneyland and is infecting people in the broader community. The bulk of the cases are in California, where one in four patients have been hospitalized. There are also several confirmed cases in Arizona, and state public health officials have warned that the outbreak has reached "a critical point."[8] For the 42 patients for whom vaccination status is known, 34 were unvaccinated and three received partial vaccinations.[9] Public health officials have emphasized that vaccination is the most important

---

[3] A Project of the College of Physicians of Philadelphia, *Measles* (online at www.historyofvaccines.org/content/timelines/measles).

[4] Centers for Disease Control and Prevention, *Measles – Q&A about Disease & Vaccine* (online at www.cdc.gov/vaccines/vpd-vac/measles/faqs-dis-vac-risks.htm).

[5] Centers for Disease Control and Prevention, *Frequently Asked Questions about Measles in the U.S.* (online at www.cdc.gov/measles/about/faqs.html).

[6] Centers for Disease Control and Prevention, *Measles Cases and Outbreaks* (online at www.cdc.gov/measles/cases-outbreaks.html).

[7] *Measles outbreak: At least 95 cases in eight states and Mexico*; Los Angeles Times (Jan. 28, 2015).

[8] *Arizona measles outbreak reaches 'critical point'*, USA Today (Jan. 28, 2015).

[9] *Measles outbreak: At least 95 cases in eight states and Mexico*; Los Angeles Times (Jan. 28, 2015).

strategy to prevent measles.[10] They have also advised caution for children under the age of 1 who are too young to be vaccinated.

We urge you to schedule a hearing on this urgent public health matter to prevent the spread of measles. Thank you for your consideration of this request.

Sincerely,

Frank Pallone, Jr.
Ranking Member

Gene Green
Ranking Member
Subcommittee on Health

Diana DeGette
Ranking Member
Subcommittee on Oversight
and Investigations

[10] *Measles Outbreak Spreads; Unvaccinated Urged To Get Vaccine*, NPR (Jan. 28, 2015).

FRED UPTON, MICHIGAN
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FOURTEENTH CONGRESS

Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115
Majority (202) 225–2927
Minority (202) 225–3641

Dr. Anne Schuchat
Director
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30333

Dear Dr. Schuchat:

Thank you for appearing before the Subcommittee on Oversight and Investigations on Tuesday, February 3, 2015, to testify at the hearing entitled "Examining the U.S. Public Health Response to Seasonal Influenza."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests with a transmittal letter by the close of business on Wednesday, March 11, 2015. Your responses should be mailed to Brittany Havens, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to brittany.havens@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Tim Murphy
Chairman
Subcommittee on Oversight and Investigations

cc: Diana DeGette, Ranking Member, Subcommittee on Oversight and Investigations

Attachments

Dr. Schuchat Questions for the Record
"Examining the U.S. Public Health Response to Seasonal Influenza"
House Energy and Commerce Subcommittee on Oversight and Investigations
February 3, 2015

The Honorable Marsha Blackburn

1. **You testified that first drifted viruses were detected on March 8, 2014. You also testified that over the summer of 2014, drifted viruses were detected in greater proportions. By September 2014, the decision was made by CDC and WHO to include one of these drifted H3N2 viruses in the Southern hemisphere vaccine. So it would seem, you would have had some idea at that point that this year's Northern hemisphere vaccine would not be as effective as in previous years.**

   About the same time that CDC was looking closely at the drifted flu virus, a Vanderbilt-led study was published. The study shows that a high-dose flu vaccine is 24% more effective in the elderly when compared to the standard dose vaccine. The researchers also concluded that the high dose vaccine is safe.

   When it became apparent that this year's vaccine would not protect well against the dominant strain of influenza, did CDC make any recommendations regarding the increase use of high-dose vaccine in the elderly?

   a. **If yes, when was that recommendation made?**
   b. **If no, can you explain why you wouldn't recommend a safe vaccine that is felt to be 24% better than baseline?**

Answer: The Advisory Committee on Immunization Practices (ACIP) has recommended high-dose inactivated vaccine (Fluzone HD, Sanofi Pasteur) since its licensure by the Food and Drug Administration (FDA) in 2009, and included the vaccine in the 2010-2011 recommendations for use in persons ≥65 years old. Adopting ACIP's recommendation, the Centers for Disease Control and Prevention (CDC) has included Fluzone HD, along with other flu vaccines, in the U.S. influenza-vaccine recommendations each season since its approval.

While this vaccine is recommended by the CDC, there is no stated preference for this vaccine over other recommended vaccines for this age group. CDC did not recommend a new national vaccine policy that stated a preference for this vaccine (or any other) once we detected that the drifted H3N2 strain was predominant because: (1) vaccination programs were well underway and many or most vaccination had already been completed by this time; (2) production of all vaccine products, including Fluzone HD, had been completed, meaning that no further doses could be made during this flu season to satisfy an increased demand created by a preferential immunization policy; and (3) the relative effectiveness of the high-dose vaccine against the specific strains circulating this season are unknown – despite one industry-supported study which found a better efficacy compared with standard dose vaccine in a previous year before the drifted strains emerged.[1]

[1] For more information, see http://www.cdc.gov/flu/protect/vaccine/qa_fluzone.htm.

2. **Moving forward, will CDC make a recommendation for a more widespread use of the high-dose flu vaccine for the elderly?**

Answer: While Fluzone HD vaccine is already recommended as an option for persons ≥65 years old, ACIP will review the data on efficacy and safety of this vaccine, and determine if amended language in the U.S. vaccine policy is warranted. Note that ACIP recommendations already state that Fluzone HD has been found to be more effective than standard dose vaccine in one study.

The Honorable Morgan Griffith

1. **Please provide all of the approximate mismatch percentages for each month from February 2014- January 2015.**

Answer:

Month	% Mismatch	% Mismatch combined*
Oct-13 Jan-14	0%	
Feb-14	1%	
Mar-14	4%	17%
Apr-14	11%	
May-14	31%	
Jun-14	6%	36%
Jul-14	34%	
Aug-14	52%	
Sep-14	30%	
Oct-14	30%	
Nov-14	61%	
Dec-14	76%	
Jan-15	69%	

*Combined mismatch is to illustrate the association with what was said during the oral testimony

The Honorable Markwayne Mullin

1. **Please provide the language and criteria that is required to declare a public health emergency.**

Answer: Under section 319 of the Public Health Service Act, 42 U.S.C. 247d, the Secretary of the Department of Health and Human Services may declare a public health emergency when she determines, after consulting with such public health officials as may be necessary, that: (1) a disease or disorder presents a public health emergency; or (2) a public health emergency, including significant outbreaks of infectious diseases or bioterrorist attacks, otherwise exists.[2]

[2] For more information about the Secretary's authority to declare a public health emergency, please see http://www.phe.gov/Preparedness/legal/Pages/phedeclaration.aspx.

FRED UPTON, MICHIGAN
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FOURTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115
Majority (202) 225-2927
Minority (202) 225-3641

February 25, 2015

Dr. Robin Robinson
Director
Biomedical Advanced Research and Development Authority
Office of the Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Robinson:

Thank you for appearing before the Subcommittee on Oversight and Investigations on Tuesday, February 3, 2015, to testify at the hearing entitled "Examining the U.S. Public Health Response to Seasonal Influenza."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, March 11, 2015. Your responses should be mailed to Brittany Havens, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to brittany.havens@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Tim Murphy
Chairman
Subcommittee on Oversight and Investigations

cc: Diana DeGette, Ranking Member, Subcommittee on Oversight and Investigations

Attachment

Dr. Robinson Questions for the Record
"Flu Preparedness and Response Efforts in the Midst of a Trying Flu Season"
House Energy and Commerce Subcommittee on Oversight and Investigations
February 3, 2015

NOTE: CONTENT AS OF MARCH 2, 2015

The Honorable Marsha Blackburn

1. Children have been hit particularly hard with the flu -- over 50 tragic deaths so far this season. I understand that the market for Tamiflu in suspension form is relatively small in the U.S. The suspension form would be needed for children. Does the CDC currently have this liquid form of Tamiflu in its stockpile?

Answer: While allowing the commercial market to accommodate general demand during the 2014-15 influenza season, the Centers for Disease Control and Prevention (CDC) Strategic National Stockpile (SNS) has 100,000 treatment courses of liquid Tamiflu™ on order for pediatric populations (**Table 1**). This product is expected to be delivered to the SNS in 2015 in order to allow the commercial market to accommodate for market demands for suspension in the 2014-2015 flu season.

For this year's influenza season, Genentech prepared 2.8 million treatment courses of liquid Tamiflu™ for U.S. distribution with over 900,000 treatment courses still available at the manufacturer and in U.S. wholesale and retail markets (**Table 2**). Thus far, supply of the oral suspension (liquid) formulation has met U.S demand during this influenza season.

Table 1. CDC/SNS inventory of Influenza Antiviral Drugs (02/23/15)

Product	Formulation	Course
Tamiflu	30mg	11.8 M
Tamiflu	45mg	3.3 M
Tamiflu	75mg	36.6 M
Tamiflu Suspension*	6mg/ml	0
Relenza	5mg	10. 7 M

*100,000 courses on order, due in Aug 2015

Table 2. Current Inventory of Tamiflu in U.S. Commercial Market (02/25/15)

Formulation	Genentech Inventory (U.S.) (in millions)	Estimated U.S. Wholesale + Retail Inventory (in millions)	Total U.S. Inventory (in millions)
75 mg (adult, capsules)	2.814	0.614	3.428
Oral Suspension (6 mg/ml bottles)	0.442	0.464	0.906
45 mg (pediatric, caps)	0.082	0.083	0.165
30 mg (pediatric, caps)	0.258	0.146	0.404
TOTALS	3.596	1.307	4.903

2. Is there an adequate amount to address a pandemic or even a severe flu season like this year if there were to be a shortage? If no, what contingency plans are in place for children who need a suspension of this medication?

Answer: Yes. As documented in Table 1 above, in addition to the pediatric suspension that is on order, there are more than 15 million treatment courses of Tamiflu™ (30mg and 45mg capsules) in the CDC/SNS that could be used for children. For children who cannot swallow, these capsules may be opened, mixed with a thick sweetened liquid (like chocolate syrup), and given that way. In addition, Tamiflu 75mg capsules may be compounded by a pharmacist to make a suspension formulation as stated in the Food and Drug Administration (FDA)-approved Tamiflu package insert (commonly done in pharmacy practice). There are also10 million treatment courses of Relenza™ presently available in the CDC/SNS that could be used for children over 5 years of age. We believe there will be a sufficient supply of influenza antiviral products for pediatric populations, including the liquid formulation, in support of pandemic preparedness within the CDC/SNS. If a shortfall is experienced, the FDA will reach out to pharmacies, as it does routinely, and directs them to make liquid formulations from encapsulated products. CDC and the Biomedical Advanced Research Development Authority (BARDA) in the Office of the Assistant Secretary for Preparedness and Response will reach out to the manufacturers and wholesalers to make more product available from U.S. and non-U.S. sources.

3. Have you had any discussions with generic manufacturers regarding a generic suspension formulation once Tamiflu loses its exclusivity in 2017?

Answer: BARDA and CDC are evaluating replenishment needs for all stockpiled antiviral drugs including Tamiflu suspension. As those evaluations continue, CDC will engage

manufacturers accordingly. We are aware that the following manufacturers are considering manufacturing generic versions of oseltamivir when the patent expires on Tamiflu™:

- Teva Pharmaceuticals, Barr Laboratories, Mylan Laboratories, and Ranbaxy Laboratories previously have stated interest in making oseltamivir;
- Cipla (INDIA) started manufacturing a generic product for the Indian market in 2008 and in 2009, which has been recognized by the World Health Organization for being as effective as oseltamivir (drug trade name Antiflu).

4. As you know, the Public Readiness and Emergency Preparedness Act, or "PREP Act", authorizes the HHS Secretary to issue a declaration that provides liability immunity to organizations that manufacture countermeasures to diseases such as influenza. In fact, there currently is a PREP Act declaration in effect for pandemic influenza vaccines, which has been extended multiple times. The current declaration is set to expire at the end of the year. In light of the ongoing public health challenges associated with pandemic influenza do you expect this PREP Act declaration to be extended before the end of the year?

Answer: The Public Readiness and Emergency Preparedness Act ("PREP Act") coverage in support of medical countermeasures for several diseases and threats, including anthrax, smallpox, botulism, nuclear, and pandemic influenza threats such as H5N1, H7N9, and other potential pandemic influenza viruses expires on December 31, 2015. HHS is reviewing options regarding the extension of PREP Act coverage past 2015.

○