FLU SEASON: U.S. PUBLIC HEALTH PREPAREDNESS AND RESPONSE

HEARING

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

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C O N T E N T S

FLU SEASON: U.S. PUBLIC HEALTH PREPAREDNESS AND RESPONSE

WEDNESDAY, DECEMBER 4, 2019

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

The subcommittee met, pursuant to call, at 10:30 a.m., in the John D. Dingell Room 2123, Rayburn House Office Building, Hon. Diana DeGette (chair of the subcommittee) presiding.

Members present: Representatives DeGette, Kennedy, Ruiz, Kuster, Castor, Tonko, Clarke, Peters, Pallone (ex officio), Guthrie (subcommittee ranking member), Burgess, McKinley, Griffith, Brooks, Mullin, Duncan, and Walden (ex officio).

Staff present: Kevin Barstow, Chief Oversight Counsel; Jesseca Boyer, Professional Staff Member; Jeffrey C. Carroll, Staff Director; Austin Flack, Staff Assistant; Waverly Gordon, Deputy Chief Counsel; Tiffany Guarascio, Deputy Staff Director; Zach Kahan, Outreach and Member Service Coordinator; Chris Knauer, Oversight Staff Director; Meghan Mullon, Staff Assistant; Tim Robinson, Chief Counsel; Nikki Roy, Policy Coordinator; Emily Ryan, GAO Detailee; Andrew Souvall, Director of Communications, Outreach and Member Services; Benjamin Tabor, Policy Analyst; C.J. Young, Press Secretary; Jen Barblan, Minority Chief Counsel, Oversight and Investigations; Brittany Havens, Minority Professional Staff Member, Oversight and Investigations; Brannon Rains, Minority Legislative Clerk; Alan Slobodin, Minority Chief Investigative Counsel, Oversight and Investigations; and Natalie Sohn, Minority Counsel, Oversight and Investigations.

Ms. DEGETTE. The Subcommittee on Oversight and Investigations hearing will now come to order.

Today, the committee is holding a hearing entitled "Flu Season: U.S. Public Health Preparedness and Response." The purpose of today's hearing is to examine the Federal Government's efforts and forecast for the 2019–2020 influenza season and ongoing influenza-related research and innovation.

The Chair now recognizes herself for purposes of an opening statement.

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

As I said, we're here this morning to discuss the topic of our Nation's preparedness for this year's flu season. Ensuring our public

health agencies have the tools they need to prepare and respond to seasonal and pandemic flu has and will remain a bipartisan effort. That's why this is the 11th hearing the committee has held related to influenza over the last 15 years. And I'm very pleased that we are having this hearing so early at the beginning of the flu season this year so we can talk about what we predict during this flu season and also encourage Americans to please, please, please go get their vaccinations.

According to the CDC, a majority of States are already seeing increased flu activity, and history has shown that we're still likely weeks away from the first peak of the season that often occurs December through February.

Today, we have the Nation's leading health experts about how people can better protect themselves and their children from this illness before peak flu season. And I want to thank all of our witnesses for being willing to come here year after year to address this important topic. I really feel like we're getting the band back together again in a way that I hope will be effective to let Americans know what's happening.

You know, we know from past flu seasons that our Nation's preparation and response efforts are critical. During the particularly severe 2017 and 2018 flu season, for example, as many as 80,000 people died as a result of the flu. So many people became sick that hospitals were forced to put tents in parking lots to treat people who had become ill.

The more recent 2018–2019 flu season was the longest one in a decade. And again, while it's still too early to tell how severe this year's flu season will be, given the unpredictability and serious nature we face, the fact that our Nation's flu vaccination rates continue to be well below our national target of 70 to 90 percent is alarming.

Last year, for example, only 63 percent of children and only 45 percent of adults received a flu vaccine. While those rates are disappointing, the fact that they are 5 to 8 points higher, respectively, compared to the year before means at least we're going in the right direction. But we have a lot more to do to protect the public health. I hope that the witnesses today can provide us an update on the efforts underway to further strengthen vaccine confidence and improve the annual vaccination rates.

I also look forward to hearing from the witnesses about the effectiveness of the flu vaccine and what research is underway to improve its efficacy. While last year's vaccine was up to 44 percent effective against the H1N1 flu strain, which was the initial flu strain that was circulating, it was only 9 percent effective for the H3N2 strain, which became the dominant strain at the end of the season.

And I know our witnesses will remind us, even a vaccine with low effectiveness is still able to protect millions of people from getting sick and help reduce the severity of symptoms for those who do. And that's why the flu vaccine remains the best tool we have to protect the public's health during these threatening times. But as I've said numerous times before, we can and will do better to improve the effectiveness.

The NIH recently began conducting the first in-human trials for a universal flu vaccine—and I'm really looking forward to hearing about that—and the National Influenza Vaccine Task Force was recently established. These developments are promising, but the importance of a strong public health infrastructure necessary to prepare for and respond to seasonal flu cannot be overstated.

I have confidence that our Federal, State, and local public health officials have put us in a strong position to respond to this year's flu season, but there's always more work to be done. And I'm looking forward to hearing from our witnesses about just what kind of work we can do.

Another issue I know that many people will be raising is the issue of producing flu vaccine here domestically in the United States, because, God forbid, we have another flu pandemic, we want to make sure that we can protect our own people.

And so, again, I'm thankful that we have such a distinguished panel today. I understand that you've brought slides, so we will not be disappointed. It's our job to—that you have the tools and the resources to remain on the cutting edge of science, and I hope today that you can tell us what you need going forward.

[The prepared statement of Ms. DeGette follows:]

PREPARED STATEMENT OF HON. DIANA DEGETTE

We are here this morning to discuss the topic of our Nation's preparedness for this year's flu season.

Ensuring our public health agencies have the tools they need to prepare and respond to seasonal and pandemic flu has, and should remain, a bipartisan effort. That's why this is the 11th hearing this committee has held related to influenza over the past 15 years.

Today, we continue the committee's long history in addressing this critical public health issue.

With the 2019–2020 flu season well underway, I thought it necessary to hold this hearing earlier than we have in past years.

According to the CDC, a majority of States are already seeing increasing flu activity. And, history has shown us that we are likely still weeks away from the first peak of the season that often occurs December through February.

Today, we are going to hear from the Nation's leading health experts about how people can better protect themselves and their children from this illness before peak flu season.

We will also hear more about the forecast for this season, as well as the efforts that are underway across the Federal Government to respond as flu activity increases.

We know from past flu seasons that our Nation's preparation and response efforts are critical.

During the particularly severe 2017–2018 flu season, for instance, as many as 80,000 people died as a result of the flu. So many people became sick that some hospitals were forced to pitch tents in parking lots to treat those who had become ill.

The more recent 2018–2019 flu season was the longest in a decade. And, while it is still too early to know exactly how severe this year's flu season will be, given the unpredictability and serious danger we face, the fact that our Nation's flu vaccination rates continue to be well below our national targets of 70 to 90 percent is highly alarming.

Last year, for example, only 63 percent of children, and just 45 percent of adults, received a flu vaccine. While those overall rates continue to be disappointing, the fact that they are 5 and 8 points higher, respectively, compared to the year before—they are, at least, moving in the right direction.

But we still have much more work to do to protect the public's health.

I am hoping that our witnesses today can provide us an update on the efforts underway to further strengthen vaccine confidence and improve these annual vaccination rates.

I also look forward to updates from our witnesses about the effectiveness of the flu vaccine, as well as what research is underway to improve its efficacy.

While last year's vaccine was up to 44 percent effective against the H1N1 flu strain, which was the initial flu strain that was circulating, it was only 9 percent effective for the H3N2 strain, which became the dominant strain at the end of season.

As I am sure our witnesses will remind us, even a vaccine with low effectiveness is still able to protect millions of people from getting sick and help reduce the severity of symptoms for those who do. And that's why the flu vaccine remains the best tool we have to protect the public's health during these threatening times.

But, as I have said numerous times before, we can and must do more to improve our vaccines' effectiveness. The NIH recently began conducting the first in-human trials for a universal flu vaccine, and the National Influenza Vaccine Task Force was recently established.

While these are certainly promising, the importance of a strong public health infrastructure necessary to prepare for, and respond to, seasonal flu cannot be overstated.

I have confidence that our Federal, State, and local public health experts have put us in a strong position to respond this year's flu season, but there is always more work to be done—and there are always things we can improve. I am looking forward to hearing from our experts today on what they believe we still need to do to make our national preparedness even stronger than it currently is.

I'm thankful that we have such a distinguished panel of experts across Federal agencies here before us today. The Nation is fortunate to have your talent on the frontlines in the ongoing fight against influenza and other infectious diseases.

It's our job to ensure that you have the tools and resources you need to remain on the cutting edge of science, and I hope today you can tell us what you need going forward.

Ms. DEGETTE. With that, I am pleased, filling in in the ranking position is the ranker on the full committee today, Mr. Walden, for 5 minutes.

OPENING STATEMENT OF HON. GREG WALDEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OREGON

Mr. WALDEN. Well, thank you, Chair DeGette, we appreciate the hearing today. As you've said, this is a longstanding bipartisan tradition of this committee to check in ahead of flu season and find out where we stand and continue to support innovation in this space and other medical device space and prescription drug space and the whole thing. When we're trying to find cures for diseases, we're all on board.

So, every year, millions of Americans put themselves at an increased risk of getting the flu because they don't get the flu vaccine. Just for the record, I have. I'm not a big guy on shots, but—you know, I do it every year, and I'm glad I do—people who don't, though, are increasing the risk for the individuals who cannot be vaccinated, including young children who are not old enough to get the flu vaccine, will get the flu. So if you've not gotten the flu vaccine yet this year—I spent a night or two in a Holiday Inn, so I'm going to play doctor here—go get the flu vaccine. If they shouldn't, I'll let our panel of real, live doctors counter me on that, but I think that would be your counsel to all of us as well.

If you think you may have the flu, please go see your doctor. There are antivirals available to reduce the symptoms you experience with the flu and shorten the duration of the flu. Great advances there.

Our senior citizens are the group at greatest risk of serious flu-related complications. According to the Centers for Disease Control and Prevention, people 65 years of age and older account for about

70 to 85 percent of seasonal flu-related deaths in recent years, and between 50 to 70 percent of seasonal flu-related hospitalizations. Seniors can get the regular flu shot or one of the two flu shots that are specifically designed for people 65 years of age or older—the high-dose flu vaccine and the adjuvanted—I'll get that—flu vaccine.

I, along with some of my fellow Republican members of the committee, sent a letter to the director of the CDC last February about improving flu vaccination coverage for seniors. We asked whether a preferential recommendation from CDC's Advisory Committee on Immunization Practices, ACIP, for vaccinating adults 65 years of age and older with a high dose or an adjuvanted influenza vaccine could reduce deaths and hospitalizations or even improve vaccination coverage. CDC told us they did not believe that there was adequate information on these vaccines to rise to a level of ACIP making a preferential recommendation.

Given what appears to be substantial evidence substantiating superior effectiveness for seniors with each of these alternatives compared to the standard-dose flu vaccine, and the preferential recommendations from other respected foreign health authorities for one of these alternatives, I do want to explore the reasons for CDC's hesitancy about supporting preferential recommendation when it appears there's real reason to believe it could help save lives.

I'm also looking forward to hearing more about research efforts to improve the flu vaccine and hopefully develop a universal flu vaccine. A universal flu vaccine would provide long-lasting protection against multiple seasonal and pandemic flu viruses, and I expect Dr. Fauci will update us on HHS' progress in implementing the strategic plan for a universal influenza vaccine that was first published in February of 2018.

Now, the President's recent Executive order promotes the development of better flu vaccines, and I support its emphasis on the need to modernize the manufacturing process for the flu vaccine. The current egg-based manufacturing process that's used for most flu vaccine doses administered in the United States takes about 22 to 24 weeks to produce the flu vaccine.

Earlier this year, advisers at the World Health Organization delayed their recommendations for the H3N2 vaccine strain to include in the flu vaccine this year by a month. And there were considerable concerns that that delay might adversely affect the vaccine supply at the beginning of this season. Thankfully, the delay did not impact the supply.

So I look forward to today's discussion. I hope to hear more about faster and more scalable manufacturing platforms, the role of antiviral drugs to mitigate the severity of the flu, and the concern over possible drug-resistant flu strains.

[The prepared statement of Mr. Walden follows:]

PREPARED STATEMENT OF HON. GREG WALDEN

Chair DeGette, thank you for having this hearing as we enter what typically is peak flu season.

Every year, millions of Americans put themselves at an increased risk of getting the flu because they do not get the flu vaccine. They also are increasing the risk that individuals who cannot be vaccinated, including young children who are not old

enough to get the flu vaccine, will get the flu. If you have not gotten the flu vaccine yet this year, please go get it today.

If you think you may have the flu, please go see your doctor. There are antivirals available to reduce the symptoms you experience with the flu and shorten the duration of the flu.

Our senior citizens are the group at greatest risk of serious flu-related complications. According to the Centers for Disease Control and Prevention, people 65 years and older account for about 70 to 85 percent of seasonal flu-related deaths in recent years and between 50 to 70 percent of seasonal-flu related hospitalizations.

Seniors can get the regular flu shot or one of two flu shots that are specifically designed for people 65 years and older—the high dose flu vaccine and the adjuvanted flu vaccine. I, along with some of my fellow Republican members on the Committee, sent a letter to the Director of the CDC last February about improving flu vaccination coverage for seniors.

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Given what appears to be substantial evidence substantiating superior effectiveness for seniors with each of these alternatives compared to the standard dose flu vaccine and the preferential recommendations from other respected foreign health authorities for one of these alternatives, I want to explore the reasons for CDC's hesitancy about supporting a preferential recommendation when there is reason to believe it could help save lives.

I am also looking forward to hearing more about research efforts to improve the flu vaccine and hopefully develop a universal flu vaccine. A universal flu vaccine would provide long-lasting protection against multiple seasonal and pandemic flu viruses, and I expect Dr. Fauci will update us on HHS' progress in implementing the Strategic Plan for a Universal Influenza Vaccine that was published in February 2018.

The President's recent Executive Order promotes the development of better flu vaccines, and I support its emphasis on the need to modernize the manufacturing process for the flu vaccine. The current egg-based manufacturing process that is used for most flu vaccine doses administered in the United States takes about 22 to 24 weeks to produce the flu vaccine. Earlier this year, advisors at the World Health Organization (WHO) delayed their recommendation for the H3N2 vaccine strain to include in the flu vaccine this year by a month, and there were concerns that this delay might affect the vaccine supply at the beginning of this season. Thankfully, the delay did not impact supply.

I look forward to today's discussion and hope to hear more about faster and more scalable manufacturing platforms, the role of antiviral drugs to mitigate the severity of flu, and the concern over possible drug-resistant flu strains. I want to thank all the witnesses for being here today. I greatly appreciate all your hard work and commitment to protecting public health.

Mr. WALDEN. With that, I would yield the balance of my time to the gentlelady from Indiana, Mrs. Brooks.

Mrs. BROOKS. Thank you, Mr. Walden.

It's been over a hundred years since the 1918 pandemic flu killed millions of people around the world, and actually, 675,000 Americans lost their lives then. Last flu season—and I think most people don't realize—61,000 Americans lost their lives, including a hundred Hoosiers.

Although the development of vaccines and drugs is a challenging process, it is so important that we continue to take action to modernize our influenza vaccines in this country.

Led by this committee, we passed PAHPA into law earlier this summer, the reauthorization of PAHPA. It established a pandemic influenza program as well as an emerging infectious disease program at BARDA to deal with known and unknown threats. The research funded by BARDA has already significantly expanded our domestic vaccine production capacity from the ability to produce

just 60 million doses of antigen influenza to the ability to produce more than 600 million doses. And with PAHPA, it supports the increase of our manufacturing capacity and our stockpile medical countermeasures, but we have much work left to do.

I want to thank all the incredible witnesses here today for your expertise. You and your teams are the ones that are going to ensure that our Nation is better prepared for pandemic flu. I look forward to hearing from our witnesses.

I yield back.

Mr. WALDEN. And I yield back.

Ms. DEGETTE. The Chair now recognizes the chairman of the full committee, Mr. Pallone, for 5 minutes for purposes of an opening statement.

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

Mr. PALLONE. Thank you, Chairwoman DeGette.

Every year, influenza causes millions of illnesses, hundreds of thousands of hospitalizations, and tens of thousands of deaths across the United States. Last year, more than a hundred children died as a result of this preventable and treatable disease, and while we're still in the early months of this year's flu season, it has already resulted in the deaths of five children.

Today, we're continuing this committee's long history of examining flu preparedness and response, and I want to thank Chairwoman DeGette in particular because I know that she annually—pretty much annually—has these hearings because she thinks it's very important. And I do want to also thank our ranking member of the full committee, Mr. Walden, for pointing out, as an example, that he had his flu shot, and I had mine too, because I think we do have to serve as an example.

The flu is one of the many preventable infectious diseases that threaten public health. We know that seasonal flu is particularly challenging to address. Flu viruses are mutating and changing constantly, and we do not yet have the ability to predict how severe flu season will be, when it will peak, or what flu strains will dominate. We also have a lot of questions about why the flu vaccine is more effective for some people and how someone's health status may affect the body's immune response.

I've been encouraged by recent efforts at the National Institutes of Health to study these issues with the goal of producing a universal flu vaccine that is effective against a broader range of flu strains. I'm also encouraged by the ongoing research supported by the Biomedical Advanced Research and Development Authority, or BARDA, and the ongoing leadership in coordination among all of the agencies testifying before us today. These efforts are vitally important.

While we wait for the results of this research, it's still critical that we continue to stress the importance of getting vaccinated every year. Thankfully, cost should no longer be a barrier for anyone to receive their annual flu vaccine. Thanks to the Affordable Care Act, flu and other immunizations are required to be covered by health insurance at no cost to the patient. The Vaccines for

Children Program has also provided free vaccinations for eligible children for nearly 25 years.

Annual flu vaccination is the best method for preventing flu and its potentially severe complications. This is true even when the flu vaccine is less effective for various strains. For example, during the 2017–2018 season, the effectiveness of that year's flu vaccine was estimated at 40 percent overall. Yet the Centers for Disease Control and Prevention estimated that it still prevented over 6 million illnesses, 91,000 hospitalizations, and 5,700 deaths.

Vaccinating yourself not only increases the odds that you won't get sick this season, but also protects everyone you come in contact with. And this is particularly important for those more vulnerable to the flu and its symptoms, such as people with chronic health conditions, older parents, or a baby niece or nephew.

And all of this demonstrates the importance of getting a flu shot, but unfortunately, 55 percent of adults were not vaccinated against the flu last season. So I look forward to hearing from the CDC about its communications and outreach strategies to increase the rates in the future.

And I know that one of the issues continues to be public confidence in vaccines, but it's critical that we continue to get the word out that vaccines are safe. While harmful misinformation campaigns continue to proliferate online and in communities across the country, the agencies must continue to spread the message of vaccine safety. And we also have to continue to improve our vaccine manufacturing process to make flu vaccines even more effective and our ability to treat patients if they do come down with the flu.

So again, I thank our witnesses for joining us, for the critical leadership role your agencies play in our Nation's flu preparedness and response efforts. And again, thank you, Chairwoman DeGette.

I yield back.

[The prepared statement of Mr. Pallone follows:]

PREPARED STATEMENT OF HON. FRANK PALLONE, JR.

Every year, Influenza causes millions of illnesses, hundreds of thousands of hospitalizations, and tens of thousands of deaths across the United States. Last year, more than 100 children died as a result of this preventable and treatable disease. And while we are still in the early months of this year's flu season, it has already resulted in the deaths of five children.

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We know that seasonal flu is particularly challenging to address. Flu viruses are mutating and changing constantly, and we do not yet have the ability to predict how severe a flu season will be, when it will peak, or what flu strains will dominate.

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We must also continue to improve our vaccine manufacturing process to make flu vaccines even more effective, and our ability to treat patients if they do come down with the flu.

I thank our witnesses for joining us today, and for the critical leadership role your agencies play in our Nation's flu preparedness and response efforts.

Ms. DEGETTE. The gentleman yields back.

The Chair now recognizes and welcomes the ranking member of the subcommittee, Mr. Guthrie, for 5 minutes.

OPENING STATEMENT OF HON. BRETT GUTHRIE, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF KENTUCKY

Mr. GUTHRIE. Thank you very much. Thank you, Chair DeGette, for holding this hearing on such an important issue.

This committee has a long history of conducting oversight of the Federal Government's response to the seasonal flu. The flu is a leading cause of death in the United States. Thousands of Americans die from flu every year, and hundreds of thousands of Americans are hospitalized.

Last flu season alone, the CDC estimates that up to 42.9 million people got sick with the flu, up to 647,000 individuals were hospitalized, and up to 61,200 individuals died from the flu. Individuals 65 years and older accounted for 90 percent of the deaths and 70 percent of the hospitalizations for the 2017–2018 flu season.

In light of this tremendous burden on our seniors, in February of this year, I, along with Republican leaders Walden and Dr. Burgess, wrote to the CDC Director about whether the CDC is doing enough to improve flu vaccine coverage and to promote high-dose and adjuvanted flu vaccines. I practiced that word twice, and I still couldn't get it out.

While we examine how to improve the response to seasonal flu, we know the best way to prevent getting the seasonal flu is to get vaccinated each season. If you have not already gotten your flu vaccine this season, please go get your flu vaccine today.

Although the flu vaccine does not have the level of effectiveness of other well-known vaccines, it is absolutely better than doing nothing. The flu vaccine saves thousands of lives each year. The flu vaccine also helps reduce severe outcomes when someone does become sick with the flu.

According to CDC data, about 80 percent of the flu associated with deaths in children have occurred in children who were not vaccinated. Moreover, a 2017 study showed that the flu vaccine also reduces severe outcomes in hospitalized patients.

I have questions today on how we can continue to improve the flu vaccine. Preliminary CDC data shows that the seasonal flu vaccine was only 29 percent effective for the 2018–2019, the lowest it has been in a decade. For more than 70 years, most flu vaccines administered in the United States have been made through the egg-based manufacturing process. We have seen some innovation over the last decade, however, with the introduction of the new manufacturing technologies, using a cell or recombinant DNA technology. Most of the flu vaccine doses distributed in the United States are still manufactured using egg-based process.

Indeed, the CDC estimates that about 82 percent of the projected vaccine supply produced for the 2019–2020 flu season will be produced using egg-based manufacturing technology, while the remaining vaccine will be produced using the cell-based and recombinant technology.

During the hearing on March 2018, Dr. Rick Bright, the HHS Deputy Secretary for Preparedness and Response, testified that we can improve the effectiveness of a vaccine in four ways: Expand domestic capacity for the cell-based and recombinant-based technologies; enhance the effective use of flu vaccines with the addition of adjuvants or higher doses of antigen; conduct clinical trials to expand vaccine in all age groups; and continue to modernize the vaccine production processes for speed and flexibility.

At that hearing, Dr. Bright noted that cell-based and recombinant-based technologies offer greater speed and flexibility than the traditional egg-based manufacturing process. And some studies have shown that they may also be more effective than egg-based vaccines.

For these reasons, I was pleased to see the President make modernizing and improving influenza vaccines a top priority through his Executive order on September 19, 2019. Modernizing flu vaccines will help protect lives through prevention and promote public health and national security.

Pandemic and seasonal flu are interdependent, and our approaches to seasonal and pandemic influenza are inextricably interwoven. What we do in one area directly impacts the other area. For example, when we expanded our domestic manufacturing capacity for pandemic response, manufacturers then also had the capacity to include an additional flu strain in the seasonal vaccine, moving from three-strain to four-strain seasonal vaccines for better coverage.

I appreciate the administration's commitment to improving our flu preparedness. I welcome all of today's witnesses, and look forward to today's discussion about how we can keep Americans

healthy during flu season and improve our Federal response to both pandemic and seasonal flu.

And I yield back.

[The prepared statement of Mr. Guthrie follows:]

PREPARED STATEMENT OF HON. BRETT GUTHRIE

hank you, Chair DeGette, for holding this hearing on such an important issue. This committee has a long history of conducting oversight of the Federal Government's response to the seasonal flu.

The flu is a leading cause of death in the United States. Thousands of Americans die from the flu every year, and hundreds of thousands of Americans are hospitalized. Last flu season alone, the CDC estimates that up to 42.9 million people got sick with the flu, up to 647,000 individuals were hospitalized, and up to 61,200 individuals died from the flu. Individuals 65 years and older accounted for 90 percent of the deaths and 70 percent of hospitalizations for the 2017–2018 flu season.

In light of this tremendous burden on our seniors, in February of this year, I, along with Republican Leaders Walden and Dr. Burgess, wrote to the CDC Director about whether the CDC is doing enough to improve flu vaccine coverage and to promote high-dose and adjuvanted flu vaccines.

While we examine how to improve the response to seasonal flu, we know the best way to prevent getting the seasonal flu is to get vaccinated each season. If you have not already gotten your flu vaccine this season, please go get your flu vaccine today.

Although the flu vaccine does not have the level of effectiveness of other well-known vaccines, it is absolutely better than doing nothing. The flu vaccine saves thousands of lives each year. The flu vaccine also helps reduce severe outcomes when someone does become sick with the flu. According to CDC data, about 80 percent of flu-associated deaths in children have occurred in children who were not vaccinated. Moreover, a 2017 study showed that the flu vaccine also reduces severe outcomes in hospitalized patients.

I have questions today on how we can continue to improve the flu vaccine. Preliminary CDC data shows that the seasonal flu vaccine was only 29 percent effective for the 2018–2019 flu season—the lowest it has been in a decade.

For more than 70 years, most of the flu vaccines administered in the United States have been made through an egg-based manufacturing process. We have seen some innovation over the last decade, however, with the introduction of new manufacturing methodologies using a cell or recombinant DNA technology.

Most of the flu vaccine doses distributed in the United States are still manufactured using the egg-based process. Indeed, the CDC estimates that about 82 percent of the projected vaccine supply produced for the 2019–2020 flu season will be produced using egg-based manufacturing technology while the remaining vaccine will be produced using cell-based and recombinant technology.

During a hearing in March 2018, Dr. Rick Bright, the HHS Deputy Assistant Secretary for Preparedness Response, testified that we could improve the effectiveness of our existing vaccines in four ways:

(1) Expand domestic capacity of the cell- and recombinant-based vaccines;

(2) Enhance the effectiveness of flu vaccines with the addition of adjuvants or higher doses of antigen;

(3) Conduct clinical trials to expand vaccine use in all age groups; and

(4) Continue to modernize the vaccine production processes for speed and flexibility.

At that hearing, Dr. Bright noted that cell-based and recombinant-based technologies offer greater speed and flexibility than the traditional egg-based manufacturing process, and some studies have shown that they may also be more effective than egg-based vaccines.

For these reasons, I was pleased to see the President make modernizing and improving influenza vaccines a top priority through his Executive order on September 19, 2019. Modernizing flu vaccines will help protect lives through prevention and promote public health and national security.

Pandemic and seasonal flu planning are interdependent, and our approaches to seasonal and pandemic influenza are inextricably interwoven. What we do in one area directly impacts the other area. For example, when we expanded our domestic manufacturing capacity for pandemic response, manufacturers then also had the capacity to include an additional flu strain in the seasonal vaccine—moving from a three strain to four strain seasonal vaccines for better coverage.

I appreciate the administration's commitment to improving our flu preparedness. I welcome all of today's witnesses and look forward to today's discussion about how

we can keep Americans healthy during flu season and improve our Federal response to both pandemic and seasonal flu.

Ms. DEGETTE. I thank the gentleman.

I ask unanimous consent that Members' written opening statements be made part of the record.

Without objection, so ordered.

I now want to introduce the witnesses for today's hearing. Dr. Nancy Messonnier, who's the Director of the National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. Welcome.

Dr. Anthony Fauci, Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Dr. Robert Kadlec, Assistant Secretary for Preparedness at U.S. Department of Health and Human Services.

And Dr. Peter Marks, Director, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration.

I want to thank—again, I thank all of you for coming before the committee. You're aware, I know, that the committee's holding an investigative hearing, and when we do so, we have the practice of taking testimony under oath.

Does anyone have an objection to testifying under oath today?

The witnesses have all responded no.

The Chair then advises you, under the rules of the House and the rules of the committee, you're entitled to be accompanied by counsel.

Does any of you wish to be accompanied by counsel?

Let the record reflect the witnesses have responded no.

If you would please rise and raise your right hand so you may be sworn in.

[Witnesses sworn.]

Ms. DEGETTE. Let the record reflect that the witnesses have responded affirmatively. And you're now under oath and subject to the penalties set forth in title 18, section 1001 of the U.S. Code.

The Chair will now recognize our witnesses for a 5-minute summary of their written statement. In front of you is the microphone and a series of lights. The timer counts down your time, and the red light turns on when your 5 minutes has come to an end.

Dr. Messonnier, you're now recognized for 5 minutes.

STATEMENTS OF NANCY MESSONNIER, M.D., DIRECTOR, NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES, CENTERS FOR DISEASE CONTROL AND PREVENTION, DEPARTMENT OF HEALTH AND HUMAN SERVICES; ANTHONY S. FAUCI, M.D., DIRECTOR, NATIONAL INSTITUTE FOR ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH; ROBERT P. KADLEC, M.D., ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE, DEPARTMENT OF HEALTH AND HUMAN SERVICES; AND PETER MARKS, M.D., DIRECTOR, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

STATEMENT OF NANCY MESSONNIER, M.D.

Dr. MESSONNIER. Good morning, Chairman DeGette, Ranking Member Guthrie, and members of the committee. I'm Dr. Nancy Messonnier, Director of the National Center for Immunization and Respiratory Diseases at CDC. And I want to thank the committee for the opportunity to discuss CDC's work to protect Americans from influenza.

Influenza is a serious and ongoing public health threat. Each year, millions of Americans get sick, hundreds of thousands require hospitalization, and tens of thousands die. The one certainty with influenza is that it is unpredictable. The virus is constantly changing and generating new flu strains that can lead to more severe flu seasons and devastating pandemics.

These changes have also allowed the virus to evade existing human immunity and require us to develop a new vaccine every single year. CDC recommends an annual flu vaccine for everyone 6 months of age and older. Influenza vaccination remains the single best way for Americans to protect themselves from the flu.

The 2019–2020 flu season has officially begun. National levels of influenza-like illness have been increasing for nearly a month, with the highest activity in the South and the West. Despite the significant benefits, the effectiveness of the flu vaccine and the number of Americans being vaccinated are not optimal. That's why we at CDC are working with our Federal colleagues to use cutting-edge science to make influenza vaccines better and ensuring providers and the public are choosing to vaccinate with confidence. This is a complicated multiyear process that must be both stepwise and iterative.

Under the recently announced Executive order to modernize influenza vaccines, CDC will work with our partners to promote new technologies to improve vaccine manufacturing and effectiveness.

While the long-lasting, broadly protective, universal vaccines that Dr. Fauci will talk about are the ultimate goal for flu prevention, these vaccines are still years away. In the nearer term, we can save millions of Americans from the flu by making incremental improvements to vaccines. If we increase vaccine effectiveness by just 5 percent, we can prevent over 17,000 additional hospitalizations in a single year.

Despite overwhelming and consistent scientific evidence that flu vaccines are safe and effective, nearly 40 percent of children and over half of adults did not receive their flu vaccine last season.

Flu vaccines are very safe. During the 2018 to 2019 flu season, nearly 170 million doses of flu vaccines were distributed nationwide. Of these, less than 0.01 percent of those receiving a vaccine reported a potential adverse event. Injection site reactions were the most commonly reported event.

CDC has a central role in every part of influenza vaccine development and administration. Over the last decade, CDC has significantly improved worldwide surveillance and characterization of influenza viruses. Global epidemiological and biological data is the foundation of the influenza vaccine virus selection and development process. We develop diagnostic assays for public health laboratories in the United States and globally, and we ship them around the world.

CDC uses next-generation sequencing to gather and analyze genomic data and share this data with other stakeholders. Genomic data help us make better decisions about what goes in each year's flu vaccine and also help us to evaluate viruses for their pandemic potential.

CDC has invested in each State public health department to have automated real-time electronic laboratory reporting of influenza test results to CDC using cloud-based messaging. CDC has supported manufacturing innovations by developing candidate vaccine viruses for the cell-based vaccine and providing genomic sequences used to make the recombinant protein vaccine.

Genomic sequencing equipment, which once filled the room, now fits in the palm of your hand. We now have a mobile mini laboratory that can be taken on a plane as a carry-on and set up almost anywhere around the world. Both cell and recombinant vaccines have the potential to be manufactured more quickly and may be more effective than traditional vaccines that are grown in eggs.

CDC was the first to establish a national system for the routine monitoring of influenza vaccine effectiveness, and we're currently expanding this network to add new immunity tests. This system provides critical information for manufacturers and researchers in developing enhanced vaccines by collecting specific data about how well the vaccine works each season in each population. CDC will continue to innovate to make incremental improvements in vaccine effectiveness and vaccine coverage.

This week is National Influenza Vaccination Week, and it is a great opportunity to remind all of you to protect yourselves and your family by making sure that you and your families get the annual flu vaccine.

Thank you for the opportunity to speak, and I'm happy to take questions.

[The prepared statement of Dr. Messonnier follows:]

Statement of Nancy Messonnier, MD
Director, National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
U.S. Department of Health and Human Services

House Committee on Energy and Commerce,
Subcommittee on Oversight and Investigations
U.S. House of Representatives

Good morning Chairwoman DeGette, Ranking Member Guthrie, and Members of the Subcommittee. I am Dr. Nancy Messonnier, Director of the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention (CDC). Thank you for the opportunity to speak with you today. CDC works collaboratively with our colleagues in other components of the Department of Health and Human Services to protect the nation's health. CDC is committed to conducting critical science, providing health information, and acting quickly to protect our nation through the control and prevention of disease, injury, and disability in the United States and globally.

Vaccines are one of public health's greatest achievements. The immunization of children in the United States (U.S.) has saved millions of lives, contributed to longer life expectancy, reduced health disparities, improved quality of life, and saved trillions of dollars in societal costs. Immunizations have become a routine part of how we care for our children, but there is more we can do to get the most benefit from this lifesaving technology, especially in regard to influenza. To protect the lives of more Americans from vaccine-preventable diseases we must continue to strengthen public trust in vaccines to further improve vaccination coverage. As we look to the upcoming flu season, we know that we have more work to do to increase the number of Americans receiving their influenza vaccination and the effectiveness of the flu vaccine.

Influenza viruses typically circulate in the United States annually, most commonly from late fall through early spring. Influenza can result in serious illness, hospitalization, and death, particularly among older adults, very young children, pregnant women, and people with certain chronic medical conditions, such as asthma, heart disease or diabetes. Influenza illness also is an important cause of missed work and school. Any flu infection can carry a risk of serious complications, hospitalization or death, even

among otherwise healthy children and adults. The recent 2017-2018 influenza season was particularly severe, causing thousands of flu-related deaths, including 186 children. The 2018-2019 season, though less severe, was record breaking in length at 21 weeks of elevated influenza activity. Influenza pandemics, which are global outbreaks of a new influenza virus, occur less frequently than seasonal epidemics, but their impacts can be even more devastating and result in millions of deaths around the globe. The 2019-2020 flu season has officially begun. National levels of influenza-like-illness have been increasing for nearly a month, however, the amount of illness still varies by region. The south and parts of the west are seeing elevated activity while other parts of the country are still seeing low activity. CDC is actively monitoring the viruses that are circulating, but it is too early to tell which viruses will predominate, or how severe the season will be. Even in seasons when the flu vaccine is less protective against the predominantly circulating strains, vaccination still reduces risk of hospitalization and death. Vaccination is the single best way for Americans to protect themselves.

CDC recommends a yearly flu vaccine for everyone 6 months of age and older as the first and most important step in protecting against this potentially serious disease. Vaccination is especially important for people at high risk of developing flu complications, and their close contacts. Influenza vaccine is very safe. Over 150 million doses of influenza vaccine are distributed each year, and CDC monitors the safety of the vaccine each and every season. During the 2018-2019 flu season, 169 million doses of influenza were distributed, with less than .01 percent of those receiving a vaccine reporting a potential adverse event associated with the vaccine. Injection site reactions were the most common type of adverse event reported. This week is National Influenza Vaccination Week, a time when CDC and our partners remind Americans that it is not too late to get a flu vaccine. As long as flu viruses are spreading and causing illness, health professionals should continue to vaccinate in order to protect as many people as possible against flu. I would like to take this opportunity to personally remind each of you to protect yourselves and your family members by getting get your annual flu vaccination.

In addition to getting a seasonal flu vaccine, you can take everyday preventive actions like staying away from sick people and washing your hands to reduce the spread of germs. If you are sick with flu, stay home from work or school to prevent spreading it to others. Prescription antiviral drugs can

be used to treat flu illness. Antiviral treatment works best when started soon after flu illness begins. When treatment is started within two days of becoming sick with flu symptoms, antiviral drugs can lessen fever and symptoms, and shorten the time you are sick by about one day. They also may reduce the risk of complications such as ear infections in children, respiratory complications requiring antibiotics, and hospitalization in adults.

CDC estimates show that flu vaccination coverage has increased over the past decade, though the increase has been more impressive in children. Vaccination among kids across all ages, 6 months through 17 years, was almost 63 percent for the 2018-2019 flu season—an increase of almost 5 percentage points from the previous season. While this is an improvement, flu vaccination coverage among children remains lower than coverage for other childhood vaccinations. A recent national study found that the most common reasons parents reported for not having their child vaccinated against influenza are concern about side-effects/safety, belief that the flu vaccine does not work well, and belief that their child is unlikely to get very sick from influenza. Influenza vaccination coverage among adults is around 45 percent, leaving more than half of adult Americans unprotected from flu each season. Although women with influenza are more than twice as likely to be hospitalized if they are pregnant, only 1 in 3 U.S. pregnant women receive both the recommended influenza (flu) and whooping cough vaccines. Despite overwhelming and consistent scientific evidence that flu vaccines are safe and effective, it is clear that continued efforts to educate providers and the general public are still needed.

CDC, and other components of the Department of Health and Humans Services (HHS), including the National Institutes of Health (NIH), Food and Drug Administration (FDA), and Biomedical Advanced Research and Development Authority (BARDA), are working together to use cutting edge science to make influenza vaccines better. This is a complicated, multi-year process that must be both stepwise and iterative. Under the recently announced Executive Order to modernize influenza vaccines, CDC will work with our other federal partners to help improve vaccine manufacturing and effectiveness. Influenza vaccines are vitally important to disease prevention, and the current production methods can be improved.

CDC has a central role in every part of the seasonal influenza vaccine development and administration cycle. The resulting data are used to provide feedback and inform policy and recommendations for new and better vaccines. CDC is the global leader in tracking and studying influenza disease and flu viruses. We have some of the world's very best scientists working on flu 24/7, and have used innovative surveillance, diagnostic, and sequencing approaches to dramatically advance what we know. However, influenza viruses are incredibly difficult to track because they constantly change. These changes are why we select new vaccine strains every year and they are also why new flu strains can emerge and lead to devastating pandemics. CDC believes that long-lasting, broadly protective "universal" vaccines are the ultimate goal for flu prevention. We are still years away from having a universal vaccine. The good news is that we think that, in the much-nearer future, we can protect millions of Americans from the flu by making incremental improvements to vaccines. These changes can be made using production platforms already available and by improving the immunization infrastructure necessary to get more Americans vaccinated each flu season.

Over the last decade, CDC has significantly improved worldwide surveillance and characterization of influenza viruses in support of more effective vaccines. Globally coordinated epidemiologic and virologic surveillance is the foundation of the influenza vaccine virus selection and development process. CDC serves as one of six World Health Organization (WHO) Collaborating Centers that receive and characterize thousands of influenza viruses each year and support core influenza staff at the WHO. CDC contributes a large amount of virus characterization and genomic sequencing data for both the U.S. and global viruses and is an innovator in new methods for the strain selection process. This process involves working across the United States and with countries all around the world to characterize many thousands of influenza viruses, which are used to inform vaccine strain selection and to develop the vaccines. CDC partnerships with more than 50 Ministries of Health and other health agencies have strengthened global influenza surveillance and created the capacities to analyze and characterize flu viruses more quickly and to increase the number of candidate vaccine viruses.

We develop diagnostic assays for public health laboratories in the United States and globally, and through our International Reagent Resource, we ship them around the world to help stop the spread of flu at its source. CDC continues to increase our ability to sequence viruses around the world – we use next generation sequencing to gather and analyze genomic data and share those data with other stakeholders. Genomic data help us make better decisions about what goes in each year's flu vaccine, and also help us evaluate viruses for their pandemic potential. We would like to be able to move completely to a domestic and global flu surveillance model that is "sequence-first," a method that uses Next Generation Sequencing (NGS) for all specimens sent to CDC for virologic surveillance. Next Generation Sequencing reveals the genetic variation among different virus particles in a single specimen and allows public health laboratorians to confirm the genetic identity of circulating viruses. These sequence data are also now a vital component of the twice-yearly WHO influenza vaccine virus strain selection process and are used in molecular modeling and forecasting. As the cost of Next Generation Sequencing drops and the availability of more rapid sequencing platforms increases, this technique may begin to serve as a routine approach for influenza virologic surveillance.

Additionally, CDC has developed and deployed a mobile mini-lab that can be carried on a plane, set up in remote, resource-limited settings to process and test specimens, and send the genomic data up to a cloud platform for further analysis and action. What was once a room full of equipment is now a device that can fit in the palm of your hand. Particularly in an outbreak setting, we can even more rapidly characterize viruses and improve detection of influenza viruses with pandemic potential. CDC can use this technology to detect other pathogens beyond flu, making it a valuable tool in resource challenged outbreak settings.

CDC has developed and maintains one of the nation's systems for monitoring the effectiveness of influenza vaccines, the U.S. Vaccine Effectiveness Network (U.S. VE Network). The U.S. VE Network currently consists of five study sites across the United States that measure the flu vaccine's effectiveness in reducing outpatient medical visits due to laboratory-confirmed influenza. This system provides critical information for manufacturers and researchers in developing enhanced vaccines by collecting more specific data about how well the vaccine works each season. Data collected through the network are instrumental in making recommendations for vaccine use, selection of new virus strains for updating

vaccines, and communication to the public on the performance of the vaccines. These data are more specific and are not available through other surveillance systems. Sustained increases in our vaccine effectiveness studies are needed to improve our understanding of how well different vaccine products work, and factors that influence how individuals respond to influenza vaccination and infection.

In the coming years, CDC will continue its collaboration with FDA, NIH, and BARDA to fight influenza through improvements in the vaccine production process, better detection and tracking of influenza illness and viruses, the development of new influenza vaccines and monitoring of vaccine effectiveness, and improvements in influenza treatment and control.

Outbreaks of vaccine preventable disease (VPDs) continue to challenge our public health system. In 2019, over 1000 cases of measles have occurred in the United States. That's more cases of measles in a single year than we've seen in the past 25 years. Nearly 75 percent of these cases can be attributed to outbreaks in New York City and New York state, which occurred in insular, close-knit communities. The outbreaks put the United States in jeopardy of losing its measles elimination status, a distinction we had maintained for nearly 20 years. This close call has led us to reframe our approach to how we protect the public from vaccine-preventable diseases, including influenza.

CDC is implementing a new strategic framework, Vaccinate with Confidence, to strengthen public trust in vaccines and prevent vaccine-preventable disease outbreaks. We are doing this through an emphasis on three key priorities: First, Protect Communities: using every tool available, we will find and protect communities at risk using tailored, targeted approaches. This includes building on CDC's work to make sure that vaccines are available, affordable, and easy-to-get in every community in the U.S. Second, Empower families. CDC will help get parents the information they need to understand the risks from vaccine-preventable diseases and the safety of vaccines to feel confident about vaccination and equip health care providers with resources to help them have effective vaccine conversations. Third, Stop myths. We will work with local partners, using trusted messengers, to establish new partnerships and contain the spread of misinformation. To advance this, we've recently collaborated with social media companies like Pinterest and Facebook. We seek to reach new groups and stakeholders to provide clear information about vaccination and the critical role it plays in protecting the American public, fortifying them from vaccine misinformation.

CDC will continue to use innovative techniques to strengthen the public's trust in vaccines and prevent disease threats such as influenza. Thank you for the opportunity to speak with you today. I am happy to answer any questions you may have.

Ms. DEGETTE. Thank you so much, Doctor.

And now, Dr. Fauci, you're recognized for 5 minutes.

STATEMENT OF ANTHONY S. FAUCI, M.D.

Dr. FAUCI. Chairperson DeGette, Ranking Member Guthrie, members of the committee, thank you for giving me the opportunity to speak to you today about the role of the National Institutes of Health in their research in addressing seasonal and pandemic flu.

If I could have the slide up, please.

[Slides are attached to Dr. Fauci's prepared statement.]

As you've heard, and many of you have mentioned, the current seasonal influenza vaccines are not consistently effective, but I want to underscore what several people have said today, that it doesn't really matter if it's a hundred percent, 50 percent, or 20 percent, it is always, always better to get vaccinated than not.

Yet we need to do better. Both the seasonal flu and the fact that pandemics do occur—we have experience that tell us it happens and will happen again. In addition, we tend to be able to chase after potential pandemics, like the H5N1, the H7N9.

This is a paper that we wrote just a little while ago, emphasizing the point that I'm—oops, it disappeared. Sorry, there you go—that we really need to do better. We need to do better in two aspects. We need to improve seasonal influenza vaccines, we need to prepare for pandemics, and we do need a universal vaccine. And that's what I want to talk about over the next couple of minutes.

As was mentioned just a while ago, we put together a strategic plan and a research agenda to develop a universal influenza vaccine and published this in February of 2018. This plan is what we call an iterative plan. By "iterative," meaning it would be a stepwise process. We are not going to get a universal flu vaccine next month or next year.

This particular slide shows what we call the two major groups of influenza vaccines—influenza A vaccines—not vaccines, but viruses.

The first group, as you see there, contains a number of influenza A's, including H1 and the prepandemic H5. Group 2 contains H3 and the prepandemic H7. When we start developing a universal influenza vaccine, we will start with getting H3N2 or H1N1, all of the iterations, and then we'll move to the next one. And that's what that pyramid, that triangle there is on the right.

The first is a highly specific vaccine, what we have today, what we're giving to people in today's vaccine. As you go down, you get broader coverage. That's what we mean when we say a universal influenza vaccine.

You mentioned the issue of egg-based and the vicissitudes associated with that. These are various vaccine platforms. By "platforms" we mean a certain mechanism whereby we have a vaccine that does not require growing the egg—growing the virus in eggs or even in cells. It's the recombinant DNA technology that you just mentioned.

Let me give you an example of how we're using that to develop a universal flu vaccine. This is a picture of the influenza virus on the left. On the right is a blowup of the hemagglutinin protein on

the surface of that virus. As you can see here, there are two components of it: a head and a stem. The vaccine induces a response predominantly against the head, which is good news, because if it works, it protects you.

However, unfortunately, that particular component of the protein mutates readily. So from season to season, it tends to drift. And that's the reason why all of us should get a vaccine every single year. When it changes a lot, we call that a shift, and that's when you get a pandemic. But note that the red dots, which mean mutations, are very few on the stem. That does not change very much.

And what investigators have done over the last few years is recognize that if you, for example—and this is just one approach to a universal flu vaccine—if you cut off the head and take that stem and put it on a nanoparticle, which is one of those platforms that I mentioned—and I have an example of one of them blown up 4 million times. This is the first example of a true universal flu vaccine that are directed against the group 1. And this was just put into clinical trial last spring, a phase 1 trial. It is currently in phase 1. We're asking about safety and does it induce a good immune response.

Next year, we will try to cover the group 2. And I hope that as you continue to have these annual hearings, we'll be able to, year after year, come back to you and talk to you about the progress of going from the top of that pyramid all the way down to a true universal influenza vaccine.

Thank you.

[The prepared statement and slide presentation of Dr. Fauci follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

The Role of the National Institutes of Health 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

National Institutes of Health

December 4, 2019

Madam Chair, Ranking Member Guthrie, and Members of the Subcommittee:

Thank you for the opportunity to discuss the role of the National Institute of Allergy and Infectious Diseases (NIAID) in the research and development of innovative influenza vaccines. NIAID is the lead institute at the National Institutes of Health (NIH) for conducting and supporting research on infectious diseases, including influenza.

NIAID supports a comprehensive portfolio of basic, translational, and clinical research on influenza. This research is focused on better understanding the influenza virus and the disease it causes as well as developing diagnostics, therapeutics, and vaccines to prevent and treat it. The constantly changing nature of seasonal influenza viruses and the threat of the emergence of a pandemic influenza necessitate the development of broadly reactive or "universal" influenza vaccines that could protect individuals over many years against multiple types of influenza viruses, both seasonal and pandemic. NIAID efforts in this regard are bolstered by ongoing collaborations with academia, philanthropic organizations, and biotechnology and pharmaceutical companies. NIAID conducts this work alongside key U.S. government partners, particularly the Department of Defense, the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response (ASPR), including the Biomedical Advanced Research and Development Authority (BARDA).

UNIQUE CHALLENGES PRESENTED BY INFLUENZA VIRUSES

Influenza viruses, particularly influenza A viruses, are persistent threats to global health as they cause significant illness and death every year in the United States and worldwide. Influenza viruses evolve and evade the immune system response in two major ways: "antigenic drift" and "antigenic shift." Antigenic drift occurs when small changes steadily accumulate in key proteins on the surface of the influenza virus. The human immune system focuses its response to influenza primarily on two proteins on the surface of the virus, hemagglutinin (HA) and neuraminidase (NA). Over time, minor alterations in the HA and NA proteins, usually resulting from genetic mutations, can impair the immune system's ability to recognize a specific influenza virus. This antigenic drift characteristic of seasonal influenza often necessitates the modification of the influenza vaccine from season to season. On the other hand, antigenic shifts are characterized by major genetic changes that, when they occur, are often manifested by the "spill over" of an influenza virus from an animal population to humans, who lack existing immunity to that virus. If these novel viruses can efficiently transmit from person to person, the risk of a potential influenza pandemic is high.

The mainstay of influenza prevention is vaccination. Seasonal influenza vaccination can protect an individual from illness, hospitalization, and death due to influenza. Current influenza vaccines are designed to protect against a few influenza strains. These vaccines result in highly "strain-specific" immunity. This means that updated influenza vaccines must be developed each year against the specific viruses that are predicted to circulate in the upcoming season. The effectiveness of seasonal influenza vaccines – a measure of how well the vaccines work to prevent influenza illness – has ranged from 10 to 60 percent in the last 15 years. This rate is

lower than that of many other licensed vaccines for common infectious diseases, such as the combined vaccine for measles, mumps, and rubella viruses, which has an effectiveness rate of 97 percent against measles. Suboptimal seasonal influenza vaccine effectiveness in part may be due to the six-month timeline required to grow the virus (usually in eggs) for production of vaccines. Once the vaccine production process is initiated, it is nearly impossible to begin anew if a different strain emerges. In years when circulating influenza strains drift significantly, mismatches between the vaccine and circulating viruses can occur, and this may result in low vaccine effectiveness.

In addition, due to the long time-frame for egg-based influenza vaccine production, vaccines likely would not be readily available if an antigenic shift occurs and a previously unidentified strain of pandemic influenza suddenly emerges. Currently, an updated – and sometimes a novel – influenza vaccine is needed for each new strain of influenza with pandemic potential. During the H1N1 influenza pandemic in 2009, a vaccine against the emergent virus strain was not available to the public until well after the peak of the pandemic had occurred. Continually "chasing" influenza viruses that jump from animals to humans comes at a substantial economic cost and can leave public health at risk. It is essential that we move beyond the current strain-specific influenza vaccine development strategy to address both seasonal and pandemic influenza.

THE NEED FOR INNOVATIONS IN INFLUENZA VACCINOLOGY

The optimal influenza vaccination strategy would deploy universal influenza vaccines that protect broadly and durably against seasonal influenza strains and those with pandemic

potential. NIAID has prioritized the development of universal influenza vaccines and has outlined its research strategy toward this goal in our *Strategic Plan for a Universal Influenza Vaccine. The Strategic Plan* focuses on three research areas: improving knowledge of the transmission, natural history, and pathogenesis of influenza infection; characterizing influenza immunity and immune factors that correlate with protection against influenza; and supporting the rational design of universal influenza vaccines. NIH will continue targeted investments in each of these research areas to generate critical information for the development of universal vaccines effective against both seasonal and pandemic influenza. Currently, we face two main challenges when designing such innovative influenza vaccines: improving vaccine production strategies and moving beyond strain-specific vaccines to vaccines with universal influenza strain coverage.

Improving Vaccine Production Strategies

Most existing influenza vaccines are produced by growing the virus in eggs. This is a time-honored, but time-consuming process. Furthermore, the vaccine undergoes a process of adaptation to grow in eggs that may in itself lead to mutations that make the resulting vaccine less effective. In recognition of these limitations, the President signed the *Executive Order on Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health* on September 19, 2019. Broadly, the Executive Order directs BARDA, CDC, NIH, and FDA to accelerate the adoption of improved influenza vaccine technologies. In alignment with the goals of the Executive Order, NIAID is conducting and supporting research to develop state-of-the-art vaccine platform technologies that could be used to develop universal influenza vaccines as well as to improve the speed and agility of the influenza vaccine manufacturing process. These platform technologies include DNA, messenger RNA (mRNA), virus-like

particles, vector-based, and self-assembling nanoparticle vaccines. For example, NIAID-supported scientists are investigating an mRNA vaccine candidate that would allow for a more rapid and flexible response to both seasonal and pandemic influenza than do existing vaccine production strategies.

Moving Beyond Strain-specific Influenza Vaccines

In addition to research into how we can improve influenza vaccine manufacturing, NIAID is working to advance from strain-specific vaccines to vaccines that would provide near universal influenza virus strain coverage. This effort aligns with NIH responsibilities outlined in the Executive Order mentioned previously. The HA protein of influenza is made up of a head and a stem, analogous to a mushroom cap and its stem. Strain-specific vaccines primarily generate an immune response to the head region, which mutates easily and differs between influenza virus strains. NIAID scientists and NIAID-supported researchers are working toward designing vaccines that generate an immune response to multiple influenza strains by targeting conserved parts of the virus – those that are less likely to differ among strains. A key target is the stem region of the HA protein, which is more similar from strain to strain than the head region of HA. The NA surface protein has been identified as another potential vaccine target. Recently, NIAID-supported scientists demonstrated in an animal model that monoclonal antibodies targeting NA of one influenza virus strain can also provide protection against several other strains of influenza. NIAID scientists also are working on new ways of displaying conserved parts of the virus to the immune system to induce a stronger and broader immune response.

The process of moving beyond strain-specific influenza vaccines will be iterative and progressive. The initial stage of development will focus on vaccines against all versions of a single subtype. For example, one vaccine may target all strains of subtype H3N2, whereas another vaccine may target all strains of subtype H1N1. All influenza A viruses fall within two broad groups. Following the initial stage, efforts would progress toward development of vaccines against all subtypes within a specific group. These vaccines would target influenza A viruses throughout either "group 1" (which includes subtypes H1N1 and H5N1, among others) or "group 2" (which includes subtypes H3N2 and H7N9, among others). The final iteration of development would provide a truly universal vaccine that would protect against all influenza A viruses.

STRATEGIES FOR DEVELOPING UNIVERSAL INFLUENZA VACCINES

NIAID is pursuing multiple strategies for the development of universal influenza vaccines that target common parts of the influenza virus in order to elicit a protective immune response against diverse influenza viruses. The NIAID Vaccine Research Center (VRC) is conducting a Phase 1 clinical trial of a universal influenza vaccine that uses a nanoparticle-based platform technology to display the stem region of the HA protein. Proteins displayed on nanoparticles are highly immunogenic. The vaccine candidate incorporates the stem region of an H1 influenza virus subtype that in animal models provided protection against influenza viruses from other subtypes within "group 1." These results suggest that vaccines targeting the stem of the HA protein could offer broader protection than existing strain-specific influenza vaccines. In 2020, VRC scientists plan to evaluate a similar nanoparticle-based vaccine candidate designed to protect against "group 2" influenza viruses. Additionally, the NIAID Division of Intramural

Research (DIR) is evaluating multiple universal influenza vaccine candidates. In collaboration with industry partners, NIAID scientists recently completed a Phase 2 clinical trial assessing a novel peptide-based candidate in a human influenza challenge model. DIR investigators also plan to launch two Phase 1 trials of other promising universal influenza vaccine candidates in early 2020. The first candidate comprises a cocktail of inactivated avian influenza viruses and the second candidate targets the NA influenza surface protein.

NIAID also supports diverse efforts by extramural researchers to develop universal influenza vaccine candidates. NIAID continues longstanding support for its Vaccine and Treatment Evaluation Units (VTEUs), which are currently conducting multiple clinical trials evaluating candidate universal influenza vaccines. In 2018, NIAID began a Phase 2 VTEU clinical trial to evaluate the M-001 vaccine candidate made by the company BiondVax that contains several influenza fragments common among multiple influenza virus strains. In addition, NIAID is sponsoring a Phase 1 VTEU clinical trial to evaluate the safety and immunogenicity of a regimen using an investigational live, attenuated intranasal influenza vaccine followed by a boost with a licensed, quadrivalent inactivated seasonal influenza vaccine. NIAID has recently expanded the capacity of the VTEUs to conduct human influenza challenge studies to assess how levels of pre-existing influenza antibodies impact the timing, magnitude, and duration of symptoms following exposure to influenza virus. These challenge studies also will facilitate the future evaluation of novel universal influenza vaccine candidates.

Recently NIAID initiated the Collaborative Influenza Vaccine Innovation Centers (CIVICs) network to foster a coordinated, multidisciplinary effort to develop more broadly

protective and longer-lasting influenza vaccines. Network researchers will conduct preclinical studies, clinical trials, and human challenge studies to explore approaches to improve seasonal and universal influenza vaccines, such as alternative vaccine platforms or new adjuvants (substances added to vaccines to boost immunity). In addition, NIAID is supporting research to examine how the immune systems of young children respond over time to their initial influenza infection and their first vaccination. These long-term cohort studies will help us understand how repeat vaccinations and immune memory affect the ability to mount an immune response to different influenza subtypes. Insights from this research will inform the design of more effective influenza vaccines and vaccination strategies.

CONCLUSION

Recent NIAID-supported advances in the areas of influenza virology, structural biology, protein engineering, immunology, and vaccinology have made possible the goal of advancing beyond strain-specific vaccines toward a universal influenza vaccine. The recent Executive Order has helped to focus and reinvigorate NIAID's longstanding partnerships with government, academic, and industry partners dedicated to the improvement of vaccines that protect against influenza. In support of the objectives of the Executive Order and guided by *the Strategic Plan for a Universal Influenza Vaccine*, NIAID will continue to accelerate research toward the development of modern vaccines that can protect against both seasonal and pandemic influenza.

Hearing of the House Energy and Commerce Committee, Subcommittee on Oversight and Investigations

The Role of the National Institutes of Health in Research Addressing Seasonal and Pandemic Influenza

Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health

December 4, 2019

National Institute of Allergy and Infectious Diseases

- **Current seasonal influenza vaccines are not consistently effective**
- **Pandemics do occur and response after the fact is not effective**
- **“Chasing after” potential pandemic outbreaks (pre-pandemic viruses) is costly and ineffective**

Influenza Vaccines: Good, but We Can Do Better

CI Paules and AS Fauci

- 15 articles discuss research toward goal of developing a universal influenza vaccine

Improving seasonal influenza vaccines

Pandemic influenza vaccines

Universal influenza vaccines

Published online
February 28, 2018

IDSA
Infectious Diseases Society of America

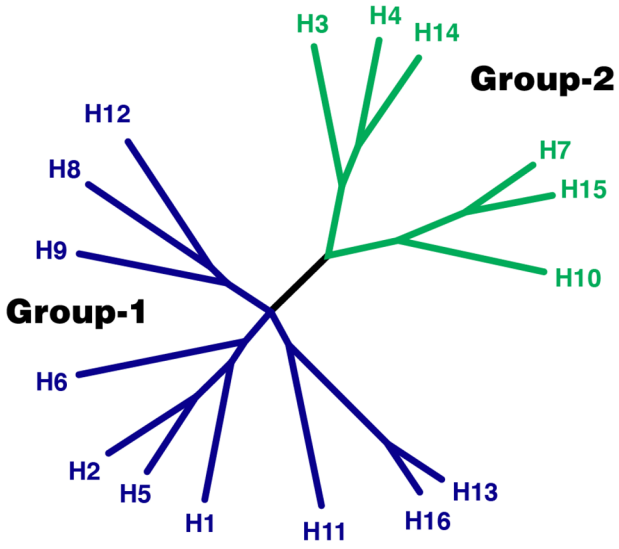
hivma
hiv medicine association

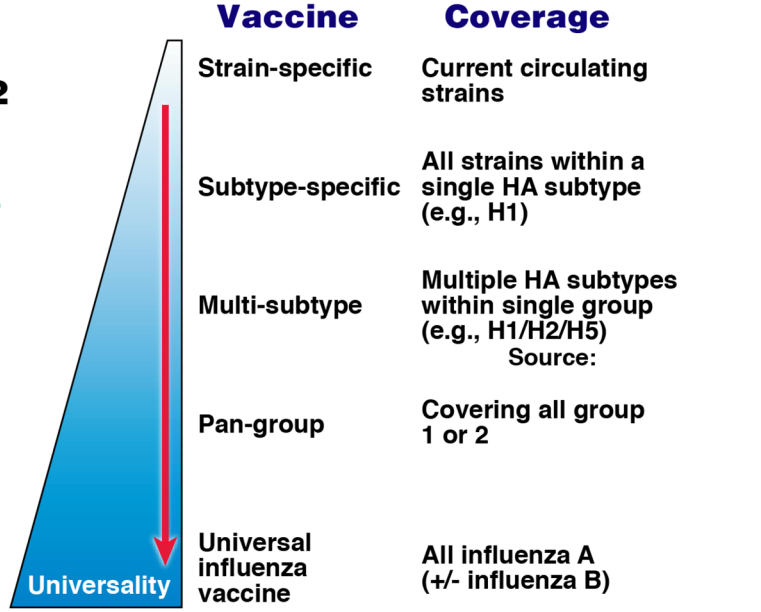
The Journal of
Infectious
Diseases

A Universal Influenza Vaccine: The Strategic Plan for the National Institute of Allergy and Infectious Diseases

EJ Erbelding, D Post, E Stemmy, PC Roberts, A Deckhut Augustine, S Ferguson, CI Paules, BS Graham, AS Fauci

Iterative Expansion of Breadth on the Path to a Universal Influenza Vaccine



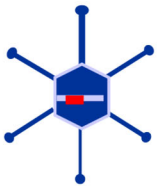


Source: Russell et al. *PNAS* 105(46), 2008;
Paules et al. *Immunity* 47(4), 2017.

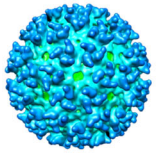
Courtesy Gary Nabel

New Platforms for Seasonal and Pandemic Influenza Vaccines

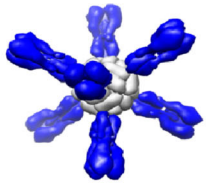
Recombinant protein



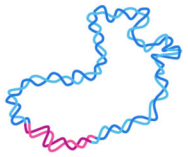
Viral vector (e.g., adenovirus)



Virus-like particle (VLP) (no RNA; non-infectious)

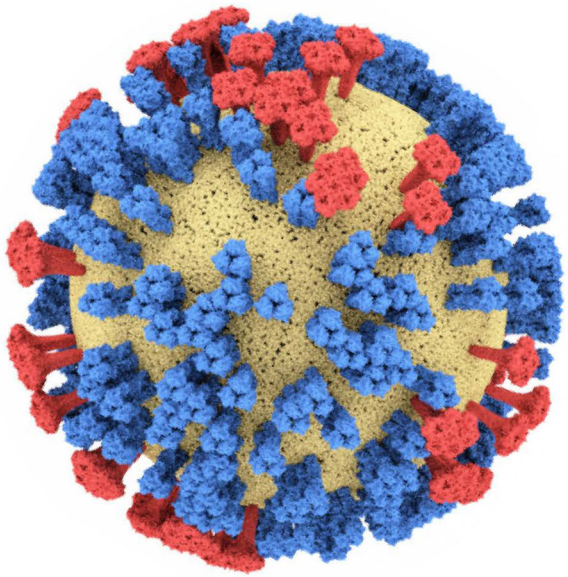


Nanoparticles (protein on particle)

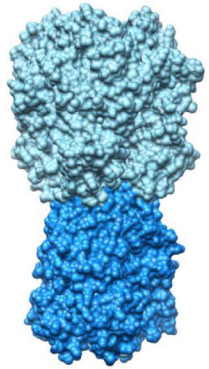


Genetic immunization (DNA and RNA vaccines)

Hemagglutinin Protein: Major Target of Influenza Vaccines



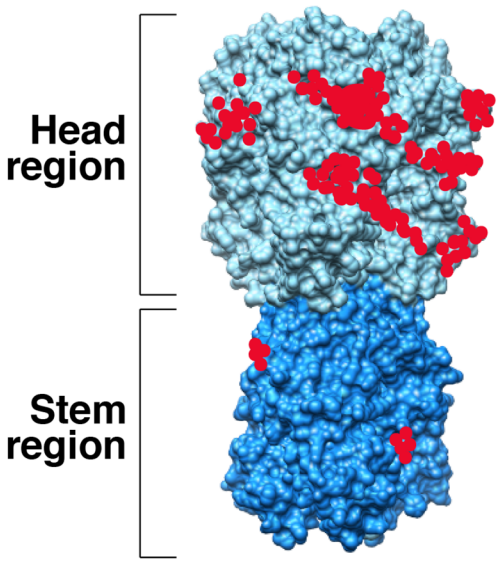
Influenza Virus



Hemagglutinin (HA) Protein

Courtesy of VRC

Influenza A Hemagglutinin (HA)



Head region

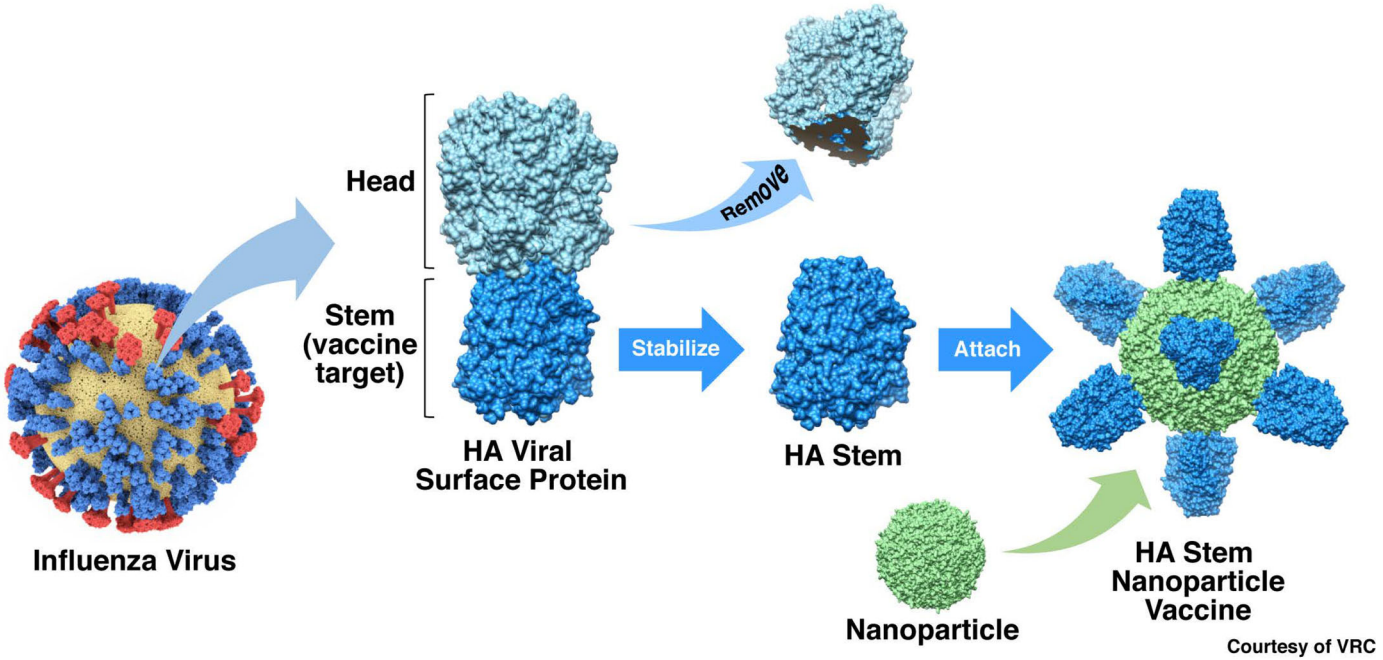
- Target of current influenza vaccines
- Differs among influenza strains
- Many mutations (●) each season

Stem region

- Target of universal influenza vaccines
- Similar among influenza strains
- Few mutations each season

Courtesy of VRC

Representative Approach to the Development of a Universal Influenza Vaccine



National Institute of Allergy and Infectious Diseases

April 3, 2019

News Release

NIH Begins First-in-Human Trial of a Universal Influenza Vaccine Candidate

Investigational vaccine designed to provide durable protection from Group 1 influenza strains

Ms. DEGETTE. Thank you so much, Dr. Fauci.
Dr. Kadlec, now you're recognized for 5 minutes.

STATEMENT OF ROBERT P. KADLEC, M.D.

Dr. KADLEC. Thank you, Chairwoman DeGette, Ranking Member Guthrie, and distinguished members of the subcommittee. Thank you for your continued commitment to flu preparedness and the opportunity to testify on our efforts to develop and rapidly manufacture effective medical countermeasures to treat influenza.

As noted, influenza is a serious threat to human health and poses a significant national security risk. Annually seasonal flu leads to hundreds of thousands of hospitalizations, tens of thousands of deaths, and costs $30 billion a year in lost productivity and healthcare costs. An influenza pandemic would be even worse, killing hundreds of thousands of Americans, costing up to $3.8 trillion.

Mitigating both seasonal and pandemic influenza is critical to saving lives, protecting Americans, and reducing the economic and healthcare burdens that result.

Before going further, I want to take a moment to thank you and your staff who worked on passing the Pandemic All-Hazard Preparedness and Advancing Innovation Act of 2019. It strengthens public health and readiness and healthcare readiness, bolsters response and recovery programs, and increases transparency.

Specific and relevant to this hearing, it authorized an annual appropriation for pandemic influenza that will ultimately enhance the confidence of private partners to invest in research, development, and manufacturing activities.

We also appreciate the past congressional supplemental appropriations for pandemic influenza preparedness, with a 2005, 2006, and 2009 supplemental appropriations. We invested in new vaccines, antivirals, domestic manufacturing, and enhanced stockpiling. Continued effort and support and funding remains critical, however.

ASPR's role in pandemic influenza preparedness has defined multiple policy documents. The 2017 HHS Pandemic Influenza Plan outlines ASPR's initiatives to prevent, control, and mitigate the effects of the influenza virus to humans. More recently, in September of this year, the White House released an Executive order on pandemic influenza preparedness. This EO identifies specific activities, many of which ASPR's already supporting with BARDA, to strengthen preparedness efforts.

Turning to preparedness initiatives, thanks to BARDA's investments, we've supported the development and approval of 23 influenza-related vaccines, antiviral drugs, devices, and diagnostics. Two significant items related to vaccine development is that now there is a licensed, cell-based influenza vaccine that can be administered to individuals 4 years and older, and a licensed recombinant DNA influenza vaccine available for persons 18 and older.

To enhance overall vaccine supply, we've supported development and licensure of adjuvanted and influenza vaccines, and during a pandemic, using adjuvants increase not only the limited vaccine supplies to protect more people, but do so faster.

To treat persons infected with influenza, we're also developing antiviral drugs. ASPR and BARDA has funded nine novel antiviral advanced development projects since 2007. To better detect the emergence of influenza, we're supporting the development of in-home and wearable diagnostics to enable patients to take responsible actions towards earlier treatment to reduce the severity of the illness and nonpharmaceutical approaches like staying home to prevent spread of the disease.

While medical countermeasures will aid in the response and potentially limit the spread, there will be a strain on our healthcare infrastructure. Since 2002, investments administered through ASPR's Hospital Preparedness Program have improved individual healthcare entities' preparedness and have built a better coordinated system.

Beginning in 2018, ASPR has supported regional partnerships to enhance capabilities above what exists at the local coalition level. The intended goal is to enable multiple healthcare systems to leverage assets and support one another when needed.

A second issue that impacts response capabilities is our dependence on medical supplies, active pharmaceutical ingredients, and raw materials from overseas. When considering the global challenges of a pandemic, this dependence would become a matter of national security. ASPR is now incorporating new technologies to support innovation for preparedness and response. An example is alternative administration approaches such as microneedle patches that deliver vaccine through the skin that could limit our dependence on imported needles and syringes and allow for faster delivery and administration of vaccine. We'll continue to look for other innovative alternatives to address our reliance on foreign supplies.

An influenza pandemic poses a significant threat to national security that could result in a significant loss of life, negatively impact the economy, and place a tremendous strain on our healthcare infrastructure. Continued support from Congress is critical to push the needle forward to best protect and respond to emerging threats.

Thank you for your time, and I look forward to discussing how we can continue to work together on this important issue, and I'll be happy to answer any questions you may have.

[The prepared statement of Dr. Kadlec follows:]

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

Flu Season: U.S. Public Health Preparedness and Response

Statement of
Robert Kadlec, MD, MTM&H, MS
Assistant Secretary For Preparedness and Response

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

For Release upon Delivery
Expected at TBD
December 4, 2019

Introduction

Chairwoman DeGette, Ranking Member Guthrie, and distinguished Members of the Subcommittee, thank you for the opportunity to testify on our efforts to develop appropriate and effective medical countermeasures to mitigate a future pandemic influenza event. I am Dr. Bob Kadlec, the Assistant Secretary for Preparedness and Response (ASPR) at the Department of Health and Human Services (HHS).

Today, I will provide background about how ASPR is partnering with the private sector to develop influenza vaccines, antivirals, and diagnostics to ensure we are as prepared for both seasonal as well as pandemic influenza. I will also provide an overview of the current challenges we face in preparedness due to dependence on active pharmaceutical ingredients (API) and other raw materials manufactured in other countries.

Pandemic Influenza: a Costly National Security Threat

Influenza has long posed a serious threat to human health. Seasonal influenza epidemics occur every year, leading to hundreds of thousands of hospitalizations and tens of thousands of deaths,[1] and billions of dollars in economic loss. In the simplest of terms, the difference between seasonal influenza and a flu pandemic is that a pandemic occurs when a new flu virus emerges that humans have little or no immunity against, allowing the virus to spread easily from person to person worldwide. A pandemic influenza event could occur at any time, potentially claiming hundreds of thousands of lives. Containing a pandemic will require an end-to-end solution: better diagnostics to detect the new virus, improved therapeutics, especially for hospitalized patients, and, perhaps most importantly, better vaccines, produced faster, and made in the United States. As noted in the White House Council of Economic Advisors' report, *Mitigating the Impact*

[1] https://www.cdc.gov/flu/about/burden/index.html

of Pandemic Influenza through Vaccine Innovation, "in a pandemic year, depending on the transmission efficiency and virulence of the particular pandemic virus, the economic damage would range from $413 billion to $3.79 trillion. Fatalities in the most serious scenario would exceed half a million people in the United States. Millions more would be sick, with between approximately 670,000 to 4.3 million requiring hospitalization."[2]

In the last decade, we have been reminded of how complex the management of seasonal and pandemic influenza is. We all remember:

- The H1N1 pandemic of 2009-2010, with severe and fatal cases among children, pregnant women, and other vulnerable populations;
- The emergence of avian influenza A(H7N9) in China in 2013, with high mortality rates in older adults, and the ensuing drifted H7N9 virus in 2017 that caused the largest recorded avian influenza outbreak and required development of a new pre-pandemic vaccine; and
- The severe H3N2 seasonal influenza virus that caused over 61,000 deaths in the United States and hospitalized hundreds of thousands more during the 2017-2018 influenza season.

ASPR's Role in Pandemic Preparedness

ASPR's mission is to save lives and protect Americans from 21st century health security threats. In addition to carrying out preparedness, response, and recovery activities within the National Response Framework (NRF) (Emergency Support Function (ESF) # 8, Public Health and Medical Services), as well as the National Disaster Recovery Framework (Health and Social Services Recovery Support Function), ASPR

[2] The Council of Economic Advisers. (2019), Mitigating the Impact of Pandemic Influenza through Vaccine Innovation, October 30, 2019, pp. 1 https://www.whitehouse.gov/wp-content/uploads/2019/09/Mitigating-the-Impact-of-Pandemic-Influenza-through-Vaccine-Innovation.pdf

also oversees advanced research, development, manufacturing capacity improvements, and procurement of medical countermeasures (MCM) against pandemics and other public health threats (e.g., vaccines, medicines, diagnostics, and other necessary medical supplies), and coordinates the manufacturing, supply chain, and stockpiling of such countermeasures. Through the Biomedical Advanced Research and Development Authority (BARDA), ASPR has supported a number of investments over the last decade to move the preparedness needle forward for protection and response to an influenza pandemic. Utilizing the supplemental funds Congress appropriated in 2005-2006 and 2009, ASPR has supported the development and production of 23 new or improved influenza vaccines, antiviral drugs, and diagnostics. Several of these products, such as cell and recombinant-based vaccines, new diagnostics, and therapeutics, are used every year to prevent, diagnose and treat seasonal influenza (or commonly known as "flu"). Other products have been licensed, and in some cases stockpiled, as pre-pandemic vaccines, ready to be rapidly formulated and distributed in the event of a pandemic.

I want to take a moment to thank all the members and their staff who worked to pass the Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019 (PAHPAIA). The new law strengthens public health and healthcare readiness, bolsters response and recovery programs, and increases transparency. In particular, there is now a formal authorization for annual funding for programs to develop medical countermeasures for pandemic influenza and other emerging infectious diseases. In the past, this funding came partly from annual appropriations in the absence of a formal authorization, and largely from supplemental appropriations after public health emergencies occurred, such as the H5N1 outbreaks in many countries in 2005, the H1N1 pandemic in 2009, the Ebola responses in 2014-2015, and the Zika response in 2016. Having an authorization of appropriations shows Congressional support for this initiative and gives private partners more confidence to research and develop products and enhance their manufacturing capacities before a disease spreads within the U.S. When an outbreak occurs, every minute counts. Developing, testing, and obtaining approval for medical countermeasures as quickly as possible, equates to saving lives; to make medical countermeasures available rapidly, we must complete these steps, to the

maximum extent possible, before the emergence of an infectious disease.

ASPR's Accomplishments to Date

President Trump signed the Executive Order on Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health on September 19, 2019. This the Executive Order (EO) directs ASPR, and three specific agencies within HHS – the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Food and Drug Administration (FDA) – to accelerate the adoption of improved influenza vaccine technologies. Specific to ASPR, the EO directs HHS to: estimate the cost of expanding and diversifying domestic vaccine-manufacturing capacity using innovative, faster, and more scalable technologies; estimate the cost of expanding domestic productions capacity of adjuvants; estimate the cost of expanding domestic fill-and-finish capacity; estimate the cost of developing, evaluating, and implementing delivery systems; evaluate incentives for the deployment and production of vaccines by private manufacturers and public-private partnerships; support, in coordination with the Departments of Defense, and Veterans Affairs, as well as with NIH a suite of clinical studies featuring different adjuvants; and, in coordination with other relevant public health agencies, research agenda to dramatically improve the effectiveness, efficiency, and reliability of influenza vaccine production. Utilizing the supplemental appropriations in 2005-2006 and 2009, ASPR has supported many efforts to build capacity and enhance overall preparedness for pandemic influenza. With the EO in place, ASPR will push forward to continue to move preparedness forward and meet the intent of the requirements included in the EO.

The traditional technology for manufacturing influenza vaccines has been egg-based. Although this method has been optimized for efficiency, it has not fundamentally changed since the 1940s – almost 80 years ago – and requires strain selection many months in advance as well as millions of eggs, which may be a

vulnerability in a pandemic. In an effort to improve the robustness and responsiveness of our vaccine manufacturing technology, ASPR began supporting the development of six different cell-based manufacturing technologies in 2006 and three different recombinant manufacturing technologies in 2009. As a result of these investments, a cell-based influenza vaccine was developed and licensed by the FDA in 2012 that can be administered to individuals four years and older. In addition, in 2013, the FDA licensed the first recombinant influenza vaccine that can be given to people 18 years of age and older.

ASPR also supported several companies in developing influenza vaccine adjuvant to enhance the effectiveness of vaccine and to reduce the overall amount of antigen needed in a dose. Adjuvant enhances the immune response, inversely limiting the amount of vaccine needed; reducing the vaccine antigen stretches supply and ultimately allows more people to be protected. The first pre-pandemic vaccine adjuvant was developed and approved by FDA in 2013. Through ASPR's efforts, the domestic capacity for both seasonal and pandemic vaccine production rose from approximately 60 million doses to over 600 million doses. Advances like this save lives and reduce costs while bolstering our domestic manufacturing capacity.

Supporting the treatment of persons infected with pandemic influenza, ASPR is working to advance development of antiviral drugs with novel mechanisms of action to reduce viral resistance, expand treatment windows, and allow for co-administration with other influenza antivirals. ASPR has funded six novel antiviral advanced development projects since 2007. One of the earliest projects supported development of intravenous (IV) peramivir, which received Emergency Use Authorization during the 2009 H1N1 pandemic. This product recently received FDA approval in 2014 as a single-dose influenza antiviral drug for treatment of uncomplicated influenza. In 2015, BARDA awarded contracts to support two new novel influenza therapeutics that have novel mechanisms of action compared to existing approved antivirals. Novel antiviral drugs, especially when used in conjunction with early identification through diagnostics, can strengthen preparedness and response levels by enabling medical and health care

professionals to effectively treat influenza disease in patients, reducing morbidity and mortality and potentially limiting the spread of disease in communities.

Lastly, to better detect the emergence of influenza, ASPR is supporting the development of in-home and wearable diagnostics to inform and empower patients to take responsible actions towards earlier treatment and non-pharmaceutical approaches to reduce the severity of illness and spread of disease. These wearable diagnostic devices will leverage advanced data analytics and algorithms coupled with innovative detection modalities to accurately and quickly diagnose patients who have been exposed to pathogens and prognosticate outcomes. The de-identified data from these individual signals will create real-time information for public health officials about outbreaks in communities. ASPR's Division of Research, Innovation, and Ventures (DRIVe) has made three awards towards this effort to date. Rapid diagnostics are a cornerstone of our strategy to protect Americans from many bacterial and viral infections; earlier diagnosis can empower patients to take action to reduce disease transmission.

While medical countermeasures will aid in the response and potentially limit the spread of an infectious disease, it is important that the health care system be as prepared as possible to treat an influx of patients. ASPR's Hospital Preparedness Program (HPP) is critical to State, local, tribal, territorial, and regional health care preparedness and response efforts. As the only source of Federal funding to prepare the nation's mostly private health care system to respond to emergencies, ASPR supports health care system readiness. With HPP grant funding, ASPR encourages diverse organizations to work together through health care coalitions (HCCs) to make sure their communities are ready to respond during emergencies. Through these investments, communities are more prepared than ever for threats to public health. Since 2002, investments administered through HPP have improved individual health care entities' preparedness and have built a system for coordinated health care system readiness.

In 2018, ASPR began supporting Regional Disaster Health Response System (RDHRS) pilot projects. These pilot projects provide funding directly to hospitals and health systems to establish multi-state regional partnerships that increase preparedness and response capability and capacity for hospitals and health care facilities in advance of, during, or immediately following incidents, including emerging infectious diseases. Two sites were selected in September 2018 to pilot the RDHRS model. In addition, in 2019 two new grants were awarded to support pilots focused on regional pediatric care. The RDHRS and pediatric cooperative agreement requirements are intentionally aligned to ensure synergy between the programs and collaboration between all sites and facilities. The lessons learned from these pilots will help health care delivery systems prepare for and respond to disasters and emergencies and aide help limit the impact of disaster.

Gaps in Preparedness

To identify potential gaps in preparedness and, where possible, make improvements, ASPR manages a robust exercise and evaluation process. Related to pandemic influenza, August 13-16, 2019, ASPR led the Crimson Contagion 2019 Functional Exercise (Crimson Contagion). Crimson Contagion exercised a nationwide pandemic influenza response, testing current plans, policies, and procedures, as well as the nation's core capability to respond. This exercise was the largest pandemic exercise to date and included 12 Federal departments/agencies, 12 states, 96 local jurisdictions, 24 Native American Tribes, 87 hospitals, and more than 100 private sector partners. The exercise found that, in the event of a pandemic:

- If vaccine development and procurement for medical countermeasures is needed above current capacity, additional funding would likely be required.
- The U.S. lacks sufficient domestic manufacturing capacity and/or raw materials for almost all pandemic influenza medical countermeasures, including vaccines and therapeutics, the needles and syringes needed to administer them, and personal protective equipment, including masks, needles, and syringes. Further, in a pandemic, global manufacturing capacity will likely not be sufficient to

meet demand, resulting in an inability to import adequate quantities of medial countermeasures.

To that point, supply chain issues are among the most significant challenges to preparing for an influenza pandemic as well as other infectious diseases. Today, we are dependent on receipt of active ingredients in America's pharmaceutical and over the counter drugs come from China and India; this dependency also extends beyond pharmaceuticals and includes auxiliary medical supplies such as syringes and gloves[3]. This dramatic shift in the manufacture of medicines is very recent in origin. In the 1990s the U.S., Europe, and Japan manufactured ninety percent of the global supply of the key ingredients for the world's medicines and vitamins. Now, China is the largest global supplier. In a pandemic environment, this dependence could become a matter of national security, as we witnessed during the H1N1 pandemic of 2009. Countries with influenza vaccine manufacturing facilities restricted exports to satisfy their domestic requirements first.

ASPR's DRIVe program and the TechWatch effort allow ASPR to partner with industry to develop innovative technologies that can help mitigate some of these concerns. The accelerator network under DRIVe improves BARDA's outreach to non-traditional partners, attracting entrepreneurs, innovators, and researchers and providing insight into working with DRIVe. The network actively identifies promising candidate technologies and introduces them to DRIVe solicitations for potential funding consideration. One current DRIVe initiative is examining the possibility of shifting vaccine delivery from needles and syringes to wearable patches. ASPR will continue to examine other alternatives in medical countermeasure development, manufacturing, distribution, and administration to continue to reduce our reliance on foreign partners.

Conclusion

[3] Gibson, Rosemary and Singh, Janardan Prasad. (2018), China Rx: Exposing the Risks of America's Dependence on China for Medicine

This committee and Congress at large have been very supportive of ASPR and our mission. Again, thank you for reauthorizing the PAHPAIA and for all the hard work that went into realizing the vision of this legislation. We could not do our job without your partnership and support.

An influenza pandemic poses a significant threat to global public health and to the security of the United States. Together with our Federal, Congressional, and our industry partners, ASPR has made major progress towards pandemic influenza preparedness. Our nation must continue to invest in domestically-based pandemic preparedness efforts and work with key global partners to prepare for, prevent, detect, and respond to emerging pandemic threats.

Thank you for your time. I look forward to discussing how we can continue to work together on this important issue.

Ms. DEGETTE. Thank you, Doctor.

Dr. Marks, now I'll recognize you for 5 minutes for an opening statement.

STATEMENT OF PETER MARKS, M.D.

Dr. MARKS. Thank you, Chair DeGette, Ranking Member Guthrie, distinguished members of the subcommittee. I'm Peter Marks, Director of the Center for Biologics Evaluation and Research at the Food and Drug Administration. Thank you for the opportunity to describe FDA's efforts, in close coordination and collaboration with its Federal partners, to ensure the development, approval, and availability of critical safe and effective medical products to address seasonal and pandemic influenza.

These products for influenza include drugs such as antiviral agents for its prevention and treatment, biologics including vaccine for prevention across the age spectrum, and devices for rapid diagnosis and supportive care.

FDA's involvement in these products spans the entire product life cycle, and the agency makes use of all of its available regulatory tools and expedited programs, including those provided by Congress, as appropriate, to help advance products critical for public health through toward approval.

Following approval, the agency monitors the safety of these products through post-market surveillance. Americans can rely on the fact that, in approving a medical product, FDA has determined that it is both safe and effective. The confidence in safety and effectiveness can be particularly important in combating increased vaccine hesitancy, which can undermine the public health benefits of vaccination.

Influenza viruses continually undergo changes in their genetic makeup. These changes can occur from one season to the next. They can also occur during influenza season. Unlike other vaccines, the composition of influenza vaccines must be updated annually so that they're effective against the predominant circulating virus that's anticipated in the upcoming influenza season.

For the 2019–2020 season, there have been more than 160 million doses of influenza vaccine produced for use in the United States, and manufacturing demands for influenza vaccines are substantial. No other vaccine is produced, FDA-approved, and distributed every year across the Nation within an approximately 6-month timeframe.

Manufacturing of the antigens to be included in the vaccines usually occurs between December and May of each year. FDA then approves the updated seasonal influenza vaccines by the end of July, and in parallel with vaccine manufacturing, FDA develops and calibrates reagents that are provided to vaccine manufacturers and our regulatory counterparts across the globe. Manufacturers and the FDA use these reagents to test the vaccines for potency and identity before FDA provides approval of the new formulation of the licensed seasonal influenza vaccines for distribution in the United States.

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 with companies on technical and manufacturing issues and conduct facility inspections, as warranted, to ensure compliance with current good manufacturing practices. The rigorous timelines currently required for vaccine production, including strain selection, reagent preparation, manufacturing of vaccine components, and formulation, fill, and distribution of the final product leave little room for error or for changes in vaccine composition after the initial strain selection process.

On the horizon are advances in manufacturing, as well as the adoption of different technologies for the production of antigen that could help compress the timeline for the production process and provide greater predictability. Certain technologies could offer more opportunity to adjust the composition of the vaccine closer in time to influenza season should a new influenza strain emerge after production has already begun.

In this regard, FDA scientists are collaborating with others to develop such needed advanced manufacturing technologies to more efficiently produce influenza virus or influenza antigen. The development adoption of such advanced manufacturing technologies has the potential to address the need for maximally efficient, agile, and flexible manufacture of both current and next-generation influenza vaccines produced according to the FDA's high standards for safety and effectiveness on which the American public relies.

Collaboration across the Federal Government is essential to meeting these challenges, and FDA looks forward to collaborating with BARDA, CDC, and NIH to implement the recent Executive order on modernizing influenza vaccines and to further accelerating the adoption of improved influenza vaccine technologies.

As we continue to invest in the future of manufacturing and vaccine technology, we also need to remember the importance of simply ensuring that more people are vaccinated, so please get your flu vaccine. And we also must work hard to ensure that products used to treat influenza, including antivirals and intravenous saline, are available and that we take steps to prevent and address shortages. As always, FDA remains committed to communicating and sharing updates with the public about all aspects of our flu response.

I look forward to answering your questions today. Thank you.

[The prepared statement of Dr. Marks follows:]

TESTIMONY

OF

PETER MARKS, M.D., PH.D.
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U.S. FOOD AND DRUG ADMINISTRATION
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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

"FLU SEASON: U.S. PUBLIC HEALTH PREPAREDNESS AND RESPONSE"

DECEMBER 4, 2019

RELEASE ONLY UPON DELIVERY

Introduction

Chair DeGette, Ranking Member Guthrie, distinguished members of the Subcommittee, I am Dr. Peter Marks, director of the Center for Biologics Evaluation and Research (CBER) at the U.S. Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to describe FDA's efforts in close coordination and collaboration with its Federal partners inside and outside of the U.S. Department of Health and Human Services to ensure the development, approval, and availability of critical safe and effective medical products to address seasonal and pandemic influenza.

These products include drugs, such as antiviral agents for the prevention and treatment of influenza; biologics, including vaccines for the prevention of influenza across the age spectrum; and devices, both for the rapid and the definitive diagnosis of influenza, as well as for supportive medical care.

FDA's role in helping to foster development, approval, and availability of safe and effective medical products

FDA involvement in these products spans the entire product lifecycle. The Agency provides scientific and regulatory advice to industry, researchers and other stakeholders across the product development spectrum, from the time prior to any formal regulatory submission is made for a product, and throughout development under FDA's investigational new drug or device exemption process.

FDA makes use of all available regulatory tools and expedited programs, including those provided by Congress, as appropriate, to help advance products critical for public health through development to approval. These programs may provide expedited timelines for review and

increased interactions between the Agency and sponsors. Americans can rely on the fact that, when it approves a medical product, FDA has determined that it is safe and effective. This confidence in a product's safety and effectiveness can be particularly important in combatting increased vaccine hesitancy, which is threatening to undermine the public health benefits of vaccination.

Following approval, the Agency uses real world data to monitor the safety of these products through both passive and active post-market surveillance. Passive surveillance involves the submission of adverse event reports by patients, providers, and manufacturers to the FDA. FDA also performs active post-market surveillance of drugs and biologics through various databases, including FDA's Sentinel system. For some of the products, such as influenza vaccine, the Agency also uses large databases in the post-market setting to evaluate vaccine effectiveness. FDA has helped validate this methodology for determination of effectiveness by comparing the results from conventional clinical trials of high dose versus standard dose seasonal influenza vaccines with data obtained in collaboration with the Centers for Medicare & Medicaid Services using their large database. This collaboration has provided valuable analysis in support of public health.

FDA also works with manufacturers of approved products to help ensure continued supply and availability of critical medical products. The Agency does this by promptly reviewing proposed technical or manufacturing changes and ensuring the continued quality of these products. In addition, FDA has several programs in place to help promote and evaluate emerging technologies that, if adopted, could result in more efficient and agile manufacturing of critical products such as the influenza vaccine. Finally, should a shortage of a medical product occur,

FDA actively works with manufacturers and other U.S. Federal agencies to address supply issues for the product in shortage.

Composition of influenza vaccines

Influenza viruses continually undergo changes in their genetic makeup. These changes can occur from one season to the next; they can also occur during an influenza season. Unlike other vaccines, the composition of influenza vaccines must be updated annually so that they are effective against the predominant circulating viruses anticipated in the upcoming influenza (or commonly known as "flu") season. The strains of virus used in vaccine production this year 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).

A Global Process for Virus Strain Selection

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 technical meetings.

To identify virus strains likely to cause illness during the upcoming influenza season, the recently-circulating influenza viruses and recent global disease patterns are studied by experts from WHO Collaborating Centers for Influenza (which include the Centers for Disease Control and Prevention (CDC)), the WHO Essential Regulatory Laboratories (this includes FDA's

Center for Biologics Evaluation and Research (CBER)), and other influenza and public health experts. In addition, blood samples from individuals receiving the most recent influenza vaccines are analyzed by the WHO Essential Regulatory Laboratories and WHO Collaborating Centers to determine how well antibodies induced by these vaccines react to recently isolated viruses.

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. WHO usually makes its vaccine strain recommendations in 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. This process, which is repeated in various other countries across the globe, is to accommodate the time that is 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. As described below, FDA takes WHO's recommendations into account as it selects strains for the upcoming influenza season.

FDA's Role in Virus Strain Selection 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. Each year, in considering the WHO recommendations, FDA brings together public health and

influenza disease experts to recommend which influenza virus strains should be included in that year's FDA-licensed vaccines. FDA convenes its Vaccines and Related Biological Products Advisory Committee (VRBPAC) each year, typically in late February or early March and within a few weeks after the WHO consultation on influenza vaccine composition to select the strains for the vaccine to be used in the Northern Hemisphere in the upcoming year. In addition to reviewing the WHO recommendations, the committee also reviews information regarding influenza virus strains that have caused human illness in the previous year, how these viruses are changing, and disease trends. The strain selection meetings for the current 2019-2020 United States influenza season took place on March 6 and March 22, 2019.

Following strain selection, influenza viruses that have been generated and accepted by WHO collaborating centers are provided to the licensed vaccine manufacturers to generate the "seed viruses" for manufacturing their influenza vaccines. FDA confirms the antigenic suitability of the manufacturer's seed viruses.

For the 2019-2020 season, there have been more than 160 million doses of influenza vaccine produced for use in the United States, and manufacturing demands for influenza vaccines are substantial. No other vaccine is produced, FDA-approved, and distributed every year across the nation within an approximately six-month time frame. The manufacturing timelines are tight and producing influenza vaccines 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 to update each licensed influenza vaccine, there is limited flexibility in the timelines for production and availability.

Manufacturing of each antigen to be included in the vaccines occurs sequentially over several months, usually from December, when it is produced at risk by manufacturers before the

strain recommendations are made, until late May. In parallel with vaccine manufacturing, FDA develops and calibrates reagents that 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 distribution in the United States.

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 facility inspections, as warranted, to ensure compliance with current good manufacturing practice requirements. The rigorous timelines currently required for vaccine production, including strain selection, reagent preparation, manufacturing of vaccine components, and formulation, fill, and distribution of the final product, leave little room for error or for changes in vaccine composition after the initial strain selection process.

Collaboration across the Federal government is essential to meeting these challenges, and FDA looks forward to continuing to work with its Federal partners to help address the public health threat caused by seasonal and pandemic influenza. In September 2019, in recognition of the limitations noted above and the importance of cross-agency collaboration, the President

signed the *Executive Order on Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health*. Broadly, the Executive Order directs the Biomedical Advanced Research and Development Authority (BARDA), CDC, the National Institutes of Health (NIH), and FDA to accelerate the adoption of improved influenza vaccine technologies.

On the horizon are advances in manufacturing, as well as the adoption of different technologies for production of antigen, that could help compress the timeline for this production process and provide greater predictability. Certain technologies could also offer more opportunity to adjust the composition of the vaccine closer in time to the influenza season, should a new influenza strain emerge after production has already begun. FDA is supporting the development of such technologies through internal work and collaborations with external researchers, with the end goal of more efficient and agile manufacturing of influenza vaccines.

FDA's Role in Influenza Vaccine Research

In addition to our important role in helping to foster vaccine development and in conducting our evaluation to determine influenza vaccine safety and effectiveness, FDA also has critical applied research functions. For example, the Agency's laboratories produce reagents crucial for influenza vaccine production. FDA is one of four WHO essential reference laboratories producing these critical reagents, including candidate viruses and potency reagents for vaccine manufacturers in both the Northern and Southern Hemispheres.

FDA also conducts applied scientific research to address current challenges in seasonal and pandemic influenza vaccine production, such as improving their effectiveness and enhancing the ability to adjust rapidly to emerging strains of influenza.

FDA scientists are collaborating with others to develop the needed advanced manufacturing technologies to more efficiently produce influenza virus or influenza antigen. The development and adoption of advanced manufacturing technologies has the potential to address the need for maximally efficient, agile and flexible manufacture of both current and next-generation influenza vaccines.

As noted by others at today's hearing, the key here is being able to produce large amounts of vaccine effective against an emerging influenza strain in a very timely manner. Producing such a vaccine against a pandemic or new seasonal influenza strain more efficiently must be done while also maintaining FDA's high standards for safety and effectiveness on which the American public relies.

Conclusion

As we continue to invest in the future of manufacturing and vaccine technology, we also need to remember the importance of simply ensuring that more people are vaccinated with available vaccines each flu season. And we also must work hard to ensure that products used to treat influenza – including antivirals and IV saline – are available, and that we take steps to prevent and address shortages.

As always, FDA remains committed to communicating and sharing updates with the public about all aspects of our flu response. I look forward to answering your questions today. Thank you.

Ms. DEGETTE. Thank you, Doctor.

Apparently, they were getting ready for the Energy and Commerce holiday party early, and they turned the lights down. They thought we should illuminate this important issue by turning the lights back up.

OK. Now it's time for the Members to ask questions, and the Chair will recognize herself for 5 minutes.

And I just want to say it's really easy to forget about the dangers that even seasonal flu can pose. We worry about pandemic flu, of course—I was telling Mr. Guthrie that keeps me up at night—but the regular flu that occurs every year, people just dismiss it as like a cold or a stomach bug, but we shouldn't lose sight of the fact that the flu is consistently one of the 10 leading causes of death in the United States, and it leads to millions of illnesses every year. As many as 61,200 people died of seasonal flu just last year.

And so, Dr. Messonnier, I wanted to ask you, briefly remind us why the seasonal flu provides such a danger to public health.

Dr. MESSONNIER. Sure, thank you. And I think that's a really great point, that people dismiss the flu and confuse it with common colds that are also circulating this year. Anybody who's had influenza can tell you that it's nothing like that, and it can be incredibly serious.

The numbers for last year are preliminary, but I think they're a great place to start. Last year's season was one of the longest seasons on record, and our estimates are 40 million cases, 19 million office visits, 576,000 hospitalizations, 45,000 deaths, and importantly, 143 children died last year from influenza, and that's really a startling number.

Ms. DEGETTE. Thank you.

Dr. Fauci, in my opening, and I know you referred to the fact that this virus mutates, sometimes even within one flu system—or flu season. Why is it so critical for us to maintain vigilance in protecting against this really unpredictable virus?

Dr. FAUCI. Well, I think you just said it, the fact that it is unpredictable means we need to be prepared, and the best way to be prepared from season to season is to develop a vaccine as closely matched to what you would predict the dominant circulating strain would be. In addition, there are other public health measures in addition that complement vaccine, such as treatment for influenza, particularly among those individuals who are at high risk for complications, such as the very young, the elderly, those with underlying conditions, pregnant women, et cetera.

We need to also do things that are public health measures. For example, if you do have the flu or your child has the flu, don't go to work, don't go to school. Make sure you don't spread it around the community.

Ms. DEGETTE. Right.

Dr. Kadlec, what keeps you up at night when you think about preparedness for the next flu—big flu outbreak?

Dr. KADLEC. Pardon me. Thank you, ma'am, I appreciate the question. I mean, I sleep like a baby, I wake up every 2 hours screaming, but——

Ms. DEGETTE. Like me.

Dr. KADLEC. Yes. But I think the key thing here is a pandemic. Quite frankly, I have unique background on this committee or this dais to have served 2 years on the Senate Intelligence Committee and looked at the many threats that face the United States. But there is no singular threat that could devastate our country through our health and our economy and our social institutions than pandemic influenza.

Ms. DEGETTE. Yes.

Dr. KADLEC. And we had four during the last century. And even though we've had a mild one in this first century, I think the risk is that we'll have another severe one, and that would devastate our country.

Ms. DEGETTE. And I know this panel has a lot more questions about that, but I'll throw that back to you, Dr. Fauci. I know this is why—one of the reasons why it's so important that we continue to innovate and to advance the vaccines. What can Congress do—what can Congress continue to do to help in these efforts to modernize and streamline the flu vaccine?

Dr. FAUCI. Well, Madam Chairperson, what you can do is what you have been doing, and it really is very important. And all of us feel very strongly in a positive way how this committee continues to come back each year and emphasize publicly the importance of this.

With regard to support, the Congress has been extremely supportive of the research efforts at the NIH, as well as the work that the CDC and other agencies do. So my direct answer to your question is just keep it up, please.

Ms. DEGETTE. OK. All right. Just because you said so.

Dr. Messonnier, I know that the chairman is going to ask you about what CDC is doing for public awareness, but maybe you can start giving me a brief answer to that.

Dr. MESSONNIER. Thank you. You know, Dr. Fauci and I were here previously talking in general about vaccines and the concerns about vaccine hesitancy in the United States. For flu, we have both concern from the public about the safety of vaccines, and we need to reassure the public as well as emphasize the importance of their providers educating their patients about the safety and effectiveness of flu vaccine. But actually, if you ask people why they don't get the flu vaccine, what's different than other vaccines is, another reason that they really reflect on this, that they don't believe the flu vaccine works.

Ms. DEGETTE. All right.

Dr. MESSONNIER. I think we have to do a better job at educating people that, even if you can still get the flu with the flu vaccine, the flu is milder, and it can prevent hospitalizations and deaths. So it's worth getting it even for a year when it's not a great——

Ms. DEGETTE. Thank you.

The Chair now recognizes the ranking member for 5 minutes for questioning.

Mr. GUTHRIE. Thank you.

I was going through trying to figure out where you've already answered some of my questions so we're all kind of on the same page on this area, which is great, but I'll—so I may be repetitive, but it's important to repeat some of these things, sometimes.

So, Dr. Kadlec, the September 19 Executive order directs HHS to estimate the cost of expanding and diversifying domestic vaccine manufacturing capacity using innovative, faster, and more scalable technologies. So, putting that into real words, why is it important for us to improve our domestic vaccine manufacturing capacity for flu? And what faster and more scalable technology would need to be used to expand and to diversify domestic capacity?

Dr. KADLEC. Well, thank you for your question, sir. And I think very simply is, the reason why domestic manufacturing is so critical, particularly for pandemics, is if there's a pandemic, everybody will be taking care of themselves. And so the fact if we're reliant on foreign suppliers for vaccines or anything else, we're likely to be at the end of that line, because they're going to be taking care of that first.

The second issue is, quite frankly, sir, is there are technologies that exist today and some that Dr. Fauci's working on, like messenger RNA that will permit faster and more better-matched vaccines to basically prevent flu, both seasonal and pandemic.

And specifically because of Congress' investments in the past, through the previous supplementals, we've developed two new vaccine technologies: one, recombinant cell culture, and the other one is recombinant DNA vaccines. And those are two very good and faster methods for producing. We have yet to know whether they are more effective than eggs. We believe so, but I think Dr. Messonnier can probably talk about some of the work that is ongoing in research, as well as Dr. Fauci to that. But those are two areas that I think we have leveraged it.

Unfortunately, those technologies do not have the capacity yet to overtake what we do with the egg-based flu vaccines.

Mr. GUTHRIE. OK. Thank you.

And again, Dr. Fauci, in your statement, you noticed that alignment with the goals of the Executive order, the National Institute of Allergy and Infectious Diseases is conducting and supporting research to develop state-of-the-art vaccine platform technologies that could be used to develop universal flu vaccines as well as improve the speed and agility of the flu vaccine manufacturing process.

So the question is, how are the vaccine platform technologies that the NIAID is currently researching different from flu vaccine production strategies?

Dr. FAUCI. Well, the platforms that I showed on one of those slides are each different way. All of them have a basis in recombinant DNA technology, but the critical issue about that is you don't need to grow the virus. And that is important, because when you grow the virus, it takes 5 to 6 months from the time you grow it, the way we do in eggs today and some in cells, and a number of things can happen when you do that. You can make a choice in February or March that this is the strain that you want to aim for for the following season, but by the time you get to the following season, it might have changed, number one.

Number two, there have been examples of when you put the virus in the egg, the virus tends to adapt to grow better in the egg, and it mutates. It's an RNA virus and it mutates readily. Most of those mutations don't mean anything. But every once in a while,

it mutates to the point that it actually changes the virus enough that it's different from what you originally put in.

So all of the platforms, be they recombinant DNA, messenger RNA, DNA, nanoparticles, viral-like particles, vectors, they all are recombinant technologies that don't require your growing the virus, and that's very important.

Mr. GUTHRIE. OK. Thank you very much. Appreciate that. That's good.

So, Dr. Marks, in March, Dr. Gottlieb testified as the Commissioner at the time, said that FDA scientists are using CMS data to look for differences in effectiveness in those receiving egg-based and cell-based vaccines, as well as differences in effectiveness in those that receive the standard dose versus a high-dose vaccine and the adjuvanted flu vaccine. What did CMS and FDA find by analyzing the Medicare data? And you can use that word if you'd like.

Dr. MARKS. I thank you very much. The adjuvanted flu vaccines—it took me about 4 years of medical school to learn how to pronounce that, so don't worry, it's OK. So thank you for that question.

The FDA's recently finished a study and published a study that was done in conjunction with Centers for Medicare and Medicaid Services, using their large database. And they looked at six seasons' worth of standard-dose versus high-dose influenza vaccine. And from that, they were able to see that, particularly in the population of individuals over 85 years old, the high-dose vaccine, season after season, had better effectiveness, and even in the population over 65, there was a tendency towards better effectiveness in that population as well.

Mr. GUTHRIE. OK. Thank you.

My time is expired. I yield back.

Ms. DEGETTE. I thank the gentleman.

The Chair now recognizes Mr. Ruiz for 5 minutes.

Mr. RUIZ. Thank you, Madam Chair.

Compassionate prevention and care must be available to everyone in this country, and as has been alluded here, many people have died due to the flu virus. Just about a year ago, in fact, this Sunday marks 1 year when Jakelin Caal, a 7-year-old girl, died in CBP custody because she did not have appropriate access to medical care. Whether or not it was the flu—I don't believe it was—but there has been several children who have died in CBP custody since then, including some from the flu.

Following Jakelin's death, I visited the place where she had been held, and I was horrified by the conditions that I witnessed: facilities so crowded you couldn't even see the floor, bodies on top of one another, especially children with soiled diapers, coughing on one another. And there wasn't appropriate access to sanitation places to wash their hands, to bathe. And these are individuals whose immune systems were always down due to the long trek and probably poor nutrition.

And as public health experts, I think you will all agree with me that such conditions create a breeding ground for a flu outbreak.

Following my visit, I wrote the Humanitarian Standards for Individuals in CBP Custody Act, which passed the House. It would en-

sure that individuals in CBP custody would have access to an initial health screening, to identify high-risk, vulnerable people, and provide appropriate intervention to prevent children and the elderly and others from dying. It would also put in place a baseline set of humanitarian public health standards such as access to clean water, proper sanitation, and personal hygiene.

I am concerned that, despite urging from physicians and physician organizations and the CDC, CBP has refused to administer flu vaccines to protect children and families in their custody.

Dr. Messonnier, CDC submitted a report regarding its investigation of respiratory illnesses in U.S. Border Patrol facilities, including findings and recommendations to the Department of Homeland Security in January, this past January of 2019. And I would like to submit this report for the record.

Dr. Messonnier, do the children and adults detained in these facilities face heightened risk of contracting influenza?

Dr. MESSONNIER. As you've said, crowded conditions tend to be a breeding ground for respiratory infectious diseases. There's no specific information right now about the risk at the border compared to elsewhere. But I think it's important to remember that CDC recommends that everybody age 6 months of age or older——

Mr. RUIZ. Right, everybody.

Dr. MESSONNIER [continuing]. Be vaccinated.

Mr. RUIZ. However, this report does state that there was higher prevalence of influenza in December 2018, January 2019, than the national average. So——

Dr. MESSONNIER. Right. That's right. So——

Mr. RUIZ [continuing]. In this report, it does, in 2019, January 2019, does show that there was higher. So——

Dr. MESSONNIER. Yes.

Mr. RUIZ [continuing]. What recommendations does CDC make to DHS specific to influenza vaccine and other related care for those detained in Border Patrol facilities?

Dr. MESSONNIER. So, as you said, CDC was asked by DHS for technical assistance in December of 2018 and January of 2019. We gave preliminary recommendations orally and then issued a written report. And the written report says that, as consistent with our general infection control guidelines, priority should be given to screening and isolation of ill migrants, early antiviral treatment, and flu vaccination for all staff.

Mr. RUIZ. Great. In fact, I'll read it here, it says, "Influenza vaccination should be implemented at the earliest feasible point of entry to allow maximum protection of migrant and potentially to reduce transmission in border facilities. Priority groups should include children aged 6 months through 18 years and pregnant women."

The term "earliest feasible point" is very important here. Are vaccines—the success rate of vaccination, is it—this is an obvious question, but is it more effective before they contract the influenza virus or after?

Dr. MESSONNIER. So it's obviously more effective when it's given before.

Mr. RUIZ. Exactly.

Dr. MESSONNIER. And I would also just point out perhaps that, you know, HHS' ORR program routinely vaccinates——

Mr. RUIZ. They do. ORR and ICE does. I'm specifically talking about CBP, and that's the point I'm making, because oftentimes, they stay there for 8, 14 days, when overcrowded conditions. So one of the reasons, perhaps they may say, "Oh, well, we want to get rid—move the children or move the individuals to the next facility," but if they contract the flu vaccine at CBP, then receiving the vaccine at ICE or ORR is not going to be helpful. So that's why the recommendation was to vaccinate them at the earliest point of entry at CBP.

And I ran out of time. Thank you.

Ms. DEGETTE. Without objection, the CDC report is entered into the record.

[The information appears at the conclusion of the hearing.]

Ms. DEGETTE. The Chair now recognizes the gentleman from West Virginia for 5 minutes.

Mr. MCKINLEY. Thank you, Ms. Chairwoman.

I think maybe, Dr. Messonnier, maybe I will focus on you. Did I—I want to make sure I heard your answer to the question why aren't—why aren't more people getting a vaccine. And I thought your answer was something about the public's concern with its effectiveness. Am I—did I state that correctly?

Dr. MESSONNIER. I think that there are three reasons why people don't get vaccinated, speaking generally. One is incorrect concern about the safety of the vaccine. A second is misunderstanding that the vaccine—about vaccine effectiveness, and the third, frankly, is access. It——

Mr. MCKINLEY. OK. Let me focus more on that third because I think the first two, I don't agree with you at all. Mildred Smith. She's your neighbor, my neighbor. Mildred Smith has no idea about the effectiveness rate. None. You in academia, and maybe in the research, you understand that, but she doesn't understand that. I'd like to try to figure out more the third issue of access, to be able to get that and how we might do that, so that leads me to the next question.

A part of that is obviously, I'm just an engineer. I don't practice medicine, so I'm curious how we work in—we seem to be working in a vacuum here in this conversation. What are they doing in Europe, for example? What's the outbreak? Do we have the same situation occur in Europe? Do they have a higher vaccination rate? Give me from a broader perspective than just the United States.

Dr. MESSONNIER. I think Europe is a broad set of countries, and different countries have different vaccination coverage. But I think many countries struggle with vaccination coverage against flu. And a lot of countries actually don't have the routine recommendation that we do or the implementation recommendation.

Mr. MCKINLEY. So you're telling me that, if I were to, you know, Google something here on Europe, I would not find anything because it's limited, or the European Union does not pull together some data?

Dr. MESSONNIER. No. I'm sorry. I misunderstood. Of course, there's data. I don't have it on top of mind, but I'm happy to provide it. But I would like to add——

Mr. MCKINLEY. Well, but I'd like to understand what they're doing in Europe about this, because I know NIH is spending a significant—maybe not enough but whatever. What are other countries doing about this? And what advances are they making towards this universal coverage, if that's a possibility?

And so what's Europe doing on universal coverage, the research in there, and then also, who are we partnering with? Who's the private-sector group, because NIH can only go so far. NIH is not going—you don't take clinicals to market. Is there someone that—are there different firms in the private sector that are showing some participation in this?

Dr. MESSONNIER. Maybe I'll just start with one fact and let Dr. Fauci go from there.

One thing just to point out is that the scientific community for influenza is incredibly collaborative. And the reason we have such great situational awareness about strains that are circulating is because countries all over the world—not only in Europe, but all over the world—gather strains of influenza, provide them to reference centers, sequence them, and that gives us the information globally about what's circulating.

Mr. MCKINLEY. OK. Dr. Fauci.

Dr. FAUCI. So with regard to the development of vaccines and the technology and the research, as with almost every aspect of medical research, the United States clearly dwarfs the other countries. However, the slide that I showed in my presentation about the strategic plan and research agenda that we put together was based on a meeting that we held in Rockville in the summer of 2017, and we had international participation.

So we have good input from people from the Far East, from China, from Europe, et cetera. But the actual work that's done, although not everything is done in the United States, an overwhelming proportion of the research and the production on the universal flu vaccine is done in United States. European countries make their own vaccine.

Mr. MCKINLEY. I hope there's more data. I'm fascinated with that subject and how it might be able to get to that curve. Let's go back to the initial. If Messonnier did not have the answer, do any of you know what kind of rates? If we only have, what, 45—whatever the rates are.

I've got to admit. I'm one of the guys cheating this—cheating death on this because, as a senior citizen, I don't get the flu vaccine, and I know I should. I know my wife does it every year, and she lectures me on this, and I just haven't gotten around to doing it.

So what are the rates in Europe? Do any of you know?

Dr. FAUCI. Yes, we do.

Mr. MCKINLEY. I figured. I didn't ask the right person.

Dr. FAUCI. In every single country—for example, I went to a meeting just a couple of months ago on a different subject in France. In France, they do not have the type of recommendation that we have here which, as Dr. Messonnier said, that everyone 6 months of age or older should be vaccinated.

In several of the top European countries, they vaccinate those who are at highest risk for complications: the young children, the

elderly, those with underlying conditions. It would be unusual for a European country to have the broad recommendation that we have of everyone 6 months of age or over to get a vaccine.

Mr. MCKINLEY. Well, I'm just—the reason I'm raising that question, and the time's up, I've gone over, is I want to understand a little bit. There in socialized medicine they have in Europe, I want to see, does that have an impact on it, if we were to implement it?

Ms. DEGETTE. So the gentleman's time has expired.

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

Ms. DEGETTE. The Chair now recognizes Mr. Kennedy for 5 minutes.

Mr. KENNEDY. Thank you, Madam Chair. I want to thank you for holding this important hearing, and the witnesses for your testimony and your service.

It's clear from what we've heard so far this morning that public health surveillance tools are critical in monitoring and responding to infectious diseases such as influenza and other outbreaks across the country.

Unfortunately, a June 2019 report by the Massachusetts Special Commission on Local and Regional Public Health found that, due to inconsistent funding for local public health agencies, my home State, like many others across the country, has limited capacity to collect and measure health data.

So, beginning with Dr. Messonnier, how does CDC and its partners help States like mine be able to track the spread of influenza from around the country as well as capture vaccination rates?

Dr. MESSONNIER. So, as you point out, public health runs on data. It's an incredibly crucial part of our programs. We do provide funding to help health departments to enable them to work with us on surveillance, and we've been really innovative. In fact, we've worked with the American Public Health Lab Association—sorry, Association of Public Health Labs—to build a data system that's electronic so that the data goes from regional reference labs to the cloud so that we can all have access to data sooner.

That being said, the flu program happens to be at the forefront of how we use data, and in general, the public health data systems are antiquated and, unfortunately, fragmented, and we really do need to think about new investments if we want the kind of solid systems that you're talking about.

Mr. KENNEDY. So, building on that, you said antiquated and fragmented. What gaps exist specifically in the collection of that data around the spread and severity of the flu virus?

Dr. MESSONNIER. Of course, what we'd all want is real-time, actionable data that can be used at every part of the public health and clinical system. We actually have a lot of data online now, and you can actually go to our flu site and look at electronic data that's posted every week that shows what the situation is in flu in every State. What you'd like to be able to do is use that same picture to click on your State and also understand vaccination coverage in every corner of your State and the capacity of the hospital system and whether hospital systems are overwhelmed.

And that's what we're working on, is trying to integrate all of that big data to give your State health officials the actionable data that they need.

Mr. KENNEDY. Dr. Kadlec, do you have any ideas on the collection of flu and pandemic data as well?

Dr. KADLEC. Sir, none beyond that has been identified for Dr. Messonnier, but I think the key thing is to what has been pointed out is that the systems are antiquated and fragmented. And there is a need to basically enhance those systems so that there is better real-time data, to Dr. Messonnier's point, to be actionable.

Mr. KENNEDY. And just to be a little more blunt then, if I can, are you suggesting that Congress—what actions would you like Congress to take? Is that funding, or is that additional structures that need to be put in place in order to flush out the system the way you would want to see it?

Dr. KADLEC. So I think, for the purposes of this conversation, I would just note that there is a multiyear budget that has been put together that looks at pandemic influenza that's required by Congress. It's a multiyear for the public health emergency medical countermeasure which identifies that we probably need about $5.7 billion to support efforts by NIH, FDA, and ASPR. But it doesn't include what CDC needs to do for surveillance and its other programs, important programs for vaccine acceptance.

So I think there's a way to capture this in a way going forward that I think would holistically represent what is needed to address this challenge broadly. We are responding to what Congress has identified in one area of this, but I think to Dr. Messonnier's point, there is a need to basically include these other very important supporting activities as part of that.

Mr. KENNEDY. So it's my understanding, Doctor, that during the 2009 H1N1 outbreak, local health departments did play a key role in the distribution of the vaccine. According to the National Association of County and City Health Officials, since 2008 local health departments have eliminated a cumulative total of more than 56,000 jobs, a decrease of about 25 percent of the public health workforce.

Doctor, how do you think ASPR is working with State and local health departments to prepare for that next flu pandemic?

Dr. KADLEC. Well, I think critically speaking, CDC has an important role to play, a principal role, and we play a supporting role. There are two grant programs that are administered by the department, one by CDC dealing specifically with local public health departments, and the one that ASPR basically administers, which is really about hospital preparedness. And those two things are critically linked in doing that together. And so we really need to work together to make sure that we capitalize on the public health infrastructure.

But you have highlighted, I think, a critical reality in the trends of local public health departments, which is not only the graying out of public health departments but certainly the support they need, subsidies at the State and local level as well as the Federal level to do this. And I think, jointly through CDC and ASPR, we can do better to do this, but I think, quite honestly, that's an area that you've highlighted that is a vulnerability.

Mr. KENNEDY. Thank you, sir. I yield back.

Ms. DEGETTE. I thank the gentleman.

The Chair now recognizes the gentlelady from Indiana for 5 minutes.

Mrs. BROOKS. Thank you, Madam Chairwoman, and thank you again for holding this very important hearing, and thank you all for your work.

I'd actually like to go back and allow Dr. Messonnier to answer. Is there anything further you'd like to say that Dr. Kadlec—and then I have some questions for Dr. Kadlec because you were nodding quite a bit. But is there anything else you would like to add?

Dr. MESSONNIER. I was nodding. I think Dr. Kadlec said most of it, but you know, it is CDC's step program that provides direct funding to States and then from States to local health departments to specifically work on preparedness capacity.

You can see this capacity used every day at local and State health departments, both to respond to the everyday emergencies, also to respond to the unexpected emergencies. And if we fail to invest in those departments, we'll obviously always come to regret it if we have to rely on them in an emergency.

Mrs. BROOKS. Thank you. Thank you.

Dr. Kadlec, I'd like to talk with you. Committee staff recently participated in a pan flu tabletop exercise with ASPR, and thank you for that participation. One of the biggest takeaways was that the U.S. lacks sufficient domestic manufacturing capacity and/or raw materials for almost all pan influenza medical countermeasures. This is very concerning.

Further, that global manufacturing capacity would not be sufficient to meet the demand, so specifically, we have concerns about the United States' supply of needles, syringes, surgical masks. That was raised during the exercise. We learned that—and I think we saw this during Ebola. Surgical masks are not made in the United States, and so there was a run on masks and other supplies during Ebola.

Can you discuss the challenges we face with respect to those supplies regarding the lack of domestic manufacturing and the volume we need versus what we currently have access to in the event of a pandemic?

Dr. KADLEC. Thank you, ma'am, for your question, and yes, it is a significant vulnerability as we look at particularly for pandemic preparedness. Eighty percent of the materials that we're counting on for—not only just for pandemic support, but generally in our healthcare system—emanate from China and India. So that's both raw materials, finished products, and active pharmaceutical ingredients.

If you had to look specifically at a couple of areas of particular concern around pandemic influenza preparedness, you would have to look at the antiviral drug supply. Again, we have about 67 million courses of about 80-million-person requirement that we have in our stockpile, and the active pharmaceutical ingredient comes from Asia at the present time.

So, once we would expend that immediate supply during a pandemic, in order to manufacture more, there is a number of generic manufacturers here domestically in the United States, but that active pharmaceutical ingredient is—it would be found in Asia and would be a critical supply material for any country, much less us.

Mrs. BROOKS. What are we doing as the Federal Government to work to address our domestic manufacturing capacity, whether for the API or——

Dr. KADLEC. Ma'am, on the issues of vaccines alone, I think the key thing is is—I can't give you the particulars, but we're going to have an announcement here shortly that will indicate some investments domestically to expand some of our new technology—newer technologies for vaccine manufacturers. And I think the key thing there is that we're actively pursuing this in accordance with the Executive order.

Obviously it's going to be a resource-limited kind of activity, but significantly beyond that we're really trying to put our arms around this vulnerability in terms of our supply chain to the other things that you mentioned: surgical masks, latex gloves, other personal protective equipment, as well as active pharmaceutical ingredients.

Mrs. BROOKS. Is it fair to say that, if we're better prepared for seasonal flu preparedness, that that would help us in the event of a pandemic?

Dr. KADLEC. Yes, ma'am.

Mrs. BROOKS. And is the H7N9 flu strain still a potential pandemic threat? And you're all nodding yes, I suppose. And is our prepandemic stockpile adequate right now relative to that?

Dr. KADLEC. Ma'am, I believe that—and I would turn to Dr. Messonnier and Dr. Fauci for their answer, but my understanding is that it's not a good match with the current circulating strains, so its utility would be limited.

Mrs. BROOKS. Dr. Fauci?

Dr. FAUCI. I agree. It's another example of the virus changing. We made a vaccine back in 2013, and we get to 2018, 2019, and it's a bit different, so it would not be a good match.

Mrs. BROOKS. And given ASPR's support for developing new antiviral products, how would adding new antivirals to the stockpile increase our preparedness? And how—what is the—what's the time that it takes and the money that it takes to add new antivirals to our stockpile?

Dr. KADLEC. Ma'am, very briefly, I think the risk that you're trying to mitigate is the risk that, over time, circulating flu strains will be resistant to what we have in our stockpile, which is Tamiflu. And currently, there is evidence of that in the world today.

The real reality is how much does it cost. Newer classes of antibiotics tend to be more expensive, and so it would be a much more significant investment in terms of replacing our existing stockpile.

And we're evaluating what's the mix that we need to have which gives us the advantage over what we have in our stockpile, what do we need to buy or purchase that would basically minimize or mitigate our risk to future strains.

Mrs. BROOKS. Thank you.

I yield back.

Ms. DEGETTE. Dr. Kadlec, I just wanted to follow up on something Mrs. Brooks asked you. You said a big announcement about domestic production is going to be made. When will that announcement be made, do you expect?

Dr. KADLEC. Ma'am, I'm hopeful by next week.

Ms. DEGETTE. By next week. OK. That will be—that will be really good. Thank you.

The Chair now recognizes Ms. Kuster for 5 minutes.

Ms. KUSTER. Thank you very much, and thank you, Madam Chair, for holding this timely hearing this week during National Influenza Vaccination Week.

In my home State of New Hampshire, 40 people lost their lives in the last flu season, and of particular concern to me is the impact on seniors. You can imagine, in the winter driving through rural New Hampshire is hard enough, but if you're an ill senior, that is really difficult. So I want to thank you all for being with us.

I want to focus in on—the seasonal flu vaccine last year was more effective for the first primary strain, but its effectiveness rate dropped significantly later in the season when the dominant strain in the United States changed. And, unfortunately, the longer season and the shift in flu strain, as I mentioned, led to 40 deaths in my State.

Dr. Fauci, what do you mean when we talk about vaccine effectiveness, and how is it measured?

Dr. FAUCI. Vaccine effectiveness is really a percent of protection based on a comparison to people who are not vaccinated. So if you have 100 percent effectiveness, which you almost never have, that would be essentially everybody gets protected who gets vaccinated. The percentage goes down as you have people who are vaccinated but who actually do get infected.

Ms. KUSTER. Have flu symptoms?

Dr. FAUCI. Right.

Ms. KUSTER. All right. And how does the effectiveness of last year's vaccine compare to those in the past? And will we—when we will know how effective this year's vaccine is?

Dr. FAUCI. Well, if you look at last year's effectiveness, you have to be careful to make sure that you can pick—that you look at H3N2 compared to H1N1 because when we vaccinate, we vaccinate against H3N2, H1N1, and B, actually two B's. So when you look at the H3N2, I believe it was 29 percent, if I'm not mistaken. It was 29 percent effective against H3N2.

And if you look at the chart—I'm speaking, but Nancy has it. If you look at the chart that the CDC puts out, they give each year what the effectiveness is. It really is a wide range. There's a very good year where you can get 60 percent.

The average is somewhere between 40, 50 percent or so. On a very bad year, you could go down to around 10 percent. When I say that, I say it with some degree of nervousness. It's still always better to get vaccinated regardless of what that percent is.

Ms. KUSTER. Well, I want to get to that with Dr. Messonnier. Why is it so important for people for whom the vaccine may currently be less effective, such as seniors, to get the flu vaccine each season?

Dr. MESSONNIER. Thank you. Maybe just to go back to a question that you asked, this one strain, the H3N2 strain, which was the strain that caused that second peak last year, happens to be a particularly difficult strain in terms of vaccine effectiveness. But, if you look historically, the range of the effectiveness of that strain

is always harder because of the reasons that Dr. Kadlec and Dr. Fauci mentioned earlier. We'll have preliminary estimates of the vaccine effectiveness, this season's vaccine, in February, and then our final estimates should be available in the summer.

The larger issue is when Dr. Fauci referred to vaccine effectiveness, but we have to remember that even if the vaccine is not perfectly effective against any influenza, it still can be effective against more severe influenza and against death. And so, even in a year where the overall vaccine effectiveness is not as great, vaccine effectiveness against more severe illness can actually be high. It's always better to get vaccinated than not.

Ms. KUSTER. So we should be encouraging our constituents to get the vaccine. The symptoms will be milder, and we should——

Dr. MESSONNIER. Everybody should get the vaccine, because today I can't totally predict what the season is going to be like, and my kids are vaccinated. My parents are vaccinated. Of course, I'm vaccinated.

Ms. KUSTER. And I will be as well. Thank you.

Dr. Marks, you stated in your testimony that the FDA conducts, quote, "applied scientific research to address current challenges in season and pandemic influenza vaccine production, including improving their effectiveness." What specific research efforts is the FDA currently engaged in to improve vaccine effectiveness rates, particularly for those populations less protected by recent flu vaccines?

Dr. MARKS. Thank you for that question. So we are engaged in research that's looking mainly to try to improve the ability to produce influenza vaccines on a rapid basis. We have some work that's going on that essentially builds off of NIH's work on trying to make a more effective vaccine.

But one of our major—the major thrust of work from FDA's perspective is trying to be able to be agile in our manufacturing, to look at things like advanced manufacturing technologies such as continuous manufacturing, which could allow us to actually have seasonal influenza or pandemic influenza vaccines produced at a much greater quantity, in a much smaller footprint, on U.S. soil in the event of a pandemic, which I think is one of the things that, as Dr. Kadlec mentioned, is important for national security.

Ms. KUSTER. Great. Thank you.

My time is up. I yield back.

Ms. DEGETTE. The Chair now yields 5 minutes to the gentleman from Texas, Mr. Burgess.

Mr. BURGESS. Thank you, and thanks to the panel for being here. I apologize. I've been upstairs at a cosmetics hearing. That's why I look so youthful.

Since I haven't been here, I haven't heard all of the questions that have been asked, so if I do something that's duplicative, I apologize about that. But Dr. Messonnier and maybe Dr. Kadlec, the issue of the vaccination at facilities for Customs and Border Protection has apparently come up. We had a hearing, I think we held a subcommittee in September, and also addressed this. I've traveled to many of the Customs and Border Protection facilities on the border in Texas, specifically Clint and the Ursula facility down

at McAllen. I actually went to the Ursula facility at McAllen with a DHS physician who was on that trip.

So, when this issue came up, I called that person and said, "Hey, does DHS not do this?" and he said no, DHS has given—and I forget the figure, and Dr. Kadlec, you may be able to supply it—but tens of thousands of doses of flu vaccine are administered by the Department of Homeland Security.

I guess the issue is, if they are in a facility that's only going to retain them for 12 to 72 hours, and then they're going to a Health and Human Services facility, and we're prominently talking about children here going to a Health and Human Services facility or an ORR facility where they will be for perhaps several weeks, I think it makes sense to do the vaccination at the ORR facility.

Now, I know there was an issue because Congress was late in supplying some supplemental funding for Department of Homeland Security. They got backed up with the number of people that were coming across the border in May and the early part of June, so people were held at CBP facilities for longer than what was ideal.

But, if the difficulty is we weren't providing DHS with the funding to do their primary job in the first place, I don't know where they were supposed to get the money to buy additional flu vaccine, but I suppose that's a separate story.

But can you talk at all about how you've coordinated with Customs and Border Protection and the Department of Homeland Security more specifically about your recommendations and what they see as their role?

Dr. MESSONNIER. Sure. And I apologize for repeating myself, but we were contacted by DHS last December, and we provided technical consultation in December and January that led to an oral report out and then a written report which was entered into the record. And what we recommended was what we would generally say, that the priority be given to infection control, identification, and isolation of the migrants, early provision of antivirals, and priority to vaccination of the DHS staff.

Our report goes on to say, as consistent with our general recommendations for everybody in the United States, we would recommend a flu vaccine for everybody 6 months of age and older at the earliest operationally feasible time.

Mr. BURGESS. So children that are held in Office of Refugee Resettlement facilities are going to receive the full complement of childhood vaccines as just part of the course. I think that's one of the things that's evolved since 2014.

Dr. MESSONNIER. That's right.

Mr. BURGESS. Because we don't know the vaccine history, we just provide the vaccines. It seems like it would make sense to provide the flu vaccine at that interval because that's done relatively early in their stay in an HHS facility.

Dr. MESSONNIER. That's correct. Children within ORR are given both the childhood vaccines and their flu vaccines, and my understanding is coverage is high. Another complication of this, as you point out, is the medical records which don't come with those children.

Mr. BURGESS. Right.

Dr. MESSONNIER. They err on the side of protecting them with the vaccine.

Mr. BURGESS. And, of course, what they do come with is the flu sometimes because they are held in less than ideal facilities referred to as stash houses on the other side of the border and then brought over when it's convenient with the coyotes or the cartels. They don't provide vaccination services on their side, and so they end up in our facilities oftentimes very, very ill.

Well, I'd like to see us do—if we're not doing a good job with coordinating between the two agencies, I'd like to see that as part of the exercise that comes out of this. Once again, my thanks to everyone who is on the panel.

Some of my favorite people in the world are on this panel, so I appreciate you being here and participating in our hearing today.

Thank you, and I yield back.

Ms. DEGETTE. I thank the gentleman.

The Chair now recognizes the gentlelady from Florida for 5 minutes.

Ms. CASTOR. Well, thank you, Chairwoman DeGette, for calling this hearing.

Drs. Messonnier and Fauci, we had the benefit of your testimony before the subcommittee earlier this year, the measles hearing where you both stressed the importance of vaccinations for infectious diseases. And I wanted to talk a little bit about that in regards to the flu, but looking at the CDC's statistics over the last 50, 60 years.

I think for measles what was remarkable was that in the 1950s and 1960s, where you had hundreds of thousands of people dying from that disease, the measles vaccine practically eradicated measles, and the big concern was now that people were skipping that vaccine, and it could make a comeback.

With flu, what really stands out are the high numbers still of people who come down with the illness, who are hospitalized and even die because—and that's largely because the flu strains change over time. Is that right?

Dr. FAUCI. Yes. Well, you compared measles with flu, which is something we discussed at the last hearing. So the measles that I, unfortunately, got infected with when I was a child is not particularly different from the measles that we have circulating right now. It just doesn't change. And that's the reason why a highly effective vaccine like measles, which is 97 percent at least effective, can essentially eliminate measles from certain parts of the world.

But influenza, we're constantly chasing it. It continually evolves. It continually mutates. And that's really the reason why we need to do better with seasonal flu vaccines, but we also need to get a universal vaccine that would cover those kinds of changes that occur.

Ms. CASTOR. And it's so heartening to hear about the progress being done there, but the current vaccines are safe and effective. I think you've all testified to that. So I'd like to focus on the availability. Dr. Messonnier, is the flu vaccine widely available currently?

Dr. MESSONNIER. Yes. Flu vaccine is widely available currently, and we watch carefully across the United States to make sure that

consumers aren't experiencing any shortages. You know, the last thing we want is for someone to show up in a doctor's office asking for the flu vaccine and be turned away because——

Ms. CASTOR. Right. And you said one of the reasons that people often skip it is the—skip the flu vaccine is because they're skeptical it's effective, and some people skip it because maybe they do run into a barrier. But I think working together over time, we've made a lot of progress on that.

Now, under the Affordable Care Act, the vaccine is covered, so it should be free if you have a policy under healthcare.gov. Most standard insurance policies cover this because everyone realizes, boy, it's a whole lot less expensive to get the flu vaccine than to miss a week or 10 days of work, or something even more serious.

I looked up for the State of Florida, the Florida Department of Health, floridahealth.gov. You can find, you can locate where your—where to get your vaccine, but it's fairly easy now. The Veterans Administration, you can get a free flu shot there. Community health centers all over your neighborhoods, you can get your flu vaccine.

Oftentimes your employers, colleges, and universities do that because that's the last thing they want, is students and professors being infected. Most grocery stores and pharmacies now, you can walk right in because I think sometimes it's a convenience. People are busy with their lives.

Are there any other barriers that we need to be working on to ensure that people—that there's not a cost barrier or just the access?

Dr. MESSONNIER. Thank you for those comments, and I think, you know, in addition to the issue with the vaccine effectiveness that Dr. Fauci talked about, certainly a big difference between where we are with measles and influenza is vaccination coverage.

And as you point out, it is a good buy for people as individuals and businesses to keep their employees safe. And health systems, we can actually show that, for example, in people over 65, it's much more effective from a cost perspective to prevent the flu than it is to take care of people once they get sick.

And I think the final thing that you were mentioning is really important, which is we need to make it easy for people to make the healthy choice for themselves and their families by making it easy for them to get the flu vaccine.

Half of adults are actually getting vaccinated outside their medical—their doctor's office. They're getting vaccinated at pharmacies and drug stores and supermarkets, and they're getting vaccinated in the workplace. Children, some States have actually had a lot of success in school-based vaccination programs where kids are vaccinated while they're in school, making it much more convenient for parents.

And one of the things that we're doing is exploring all of those strategies to see what we can do again to make it easy for people to make healthy decisions.

Ms. CASTOR. Well, I've had my flu shot, and everyone in my office, we have a Let's Get Our Flu Shot Day, and everyone—we apply a little peer pressure for those that might need it because it's so important. We want everyone to be healthy and well. And if you

haven't gotten your flu shot yet, you better go out today and go ahead and do that.

Thank you.

Ms. DEGETTE. I thank the gentlelady.

The Chair now recognizes the gentleman from Virginia for 5 minutes.

Mr. GRIFFITH. Thank you very much, Madam Chair.

Congresswoman Castor set up one of my questions very well, Dr. Messonnier. She said that, you know, you can go to the VA and get your shot. Most of the studies that have been done on the—let me make sure I get the wording correct—the high-dose vaccine have shown that it's much more effective for people over the age of 65, which was a part of your answer back to her. But, because the CDC has not made that a preferred—let me make sure I get—a preferred recommendation, the VA hospitals can't give that to people over 65, so they have to go somewhere else. A lot of doctors are giving it, but the VA can't give it.

So, that being said, with the studies out there, what do we need to do to get the CDC to make this a preferred recommendation for the high-dose flu vaccine, because it looks like we're—you know, she mentioned it, not knowing I was going in this direction, that a lot of people go to the VA hospital and a lot of our veterans do.

But if you're over the age of 65, you probably ought to be getting this not-yet-CDC-preferred treatment, but the high-dose vaccine, but you're not able to get it there.

Dr. MESSONNIER. Actually, thank you for the opportunity to comment on this. There are actually nine different flu vaccines available this season, and eight of those are licensed for people over 65. So the complication is the comparison of every single one of those products to know which ones are better and which ones are not.

CDC, as I expect you would not be surprised, is understandably cautious about making preferential recommendations because we need to be sure that a vaccine that we're going to prefer is not just effective this season but is effective, is preferential, better, every season. And since every flu season is so different, we tend to be cautious.

That being said, we're taking this issue very seriously. Since last year, we've launched new, more robust studies to examine the vaccines that are available in this age group, and we have an interagency working group with our Federal partners so that we can make sure that we're covering all the watershed of all the studies that need to be done.

We've also put this back to our advisory committee to ask them to look again at the available data and consider this issue. The issue will be considered as all of these issues are in our public meeting where folks can see the debate and see how they come—you know, what conclusions they come to.

So we take the issue very seriously, but again, understandably cautious about making a recommendation like that.

Mr. GRIFFITH. But you said eight of the nine are actually considered preferred.

Dr. MESSONNIER. No, licensed. Of the nine available vaccines, eight of them are licensed for people over 65.

Mr. GRIFFITH. OK. But this is dealing with the high-dose vaccine, and according to the data I have here, there have been 14 studies over nine consecutive seasons, 14 million study participants, and only one of those studies did not say that it was preferred or that it was better for people over the age of 65 to get the high-dose vaccine.

Dr. MESSONNIER. So that is a comparison of one company's high-dose vaccine against the same company's regular dose vaccine.

Mr. GRIFFITH. Uh-huh.

Dr. MESSONNIER. The problem is that there are more than one high-dose vaccine and also adjuvanted vaccines in that age group. The other issue, back to the issue Dr. Fauci was talking about, is that we need to make sure that it's preferential—that it's more effective against every one of the potential strains of flu vaccine, which means we need more robust data, not just effectiveness against H1N1 but against H3N2 and both types of B, be confident that a preferential recommendation will be right every single season.

Mr. GRIFFITH. Well, in the absence of a preferential recommendation, can you work with the VA? Will you work with the VA to ensure that our veterans over age 65 can receive the high-dose vaccine if their doctor thinks that's appropriate?

Dr. MESSONNIER. We're obviously always happy to work with the VA, and they are a part of this interagency working group where we're really robustly trying to get the data together to look at this issue really seriously.

Mr. GRIFFITH. Because outside of the VA, a lot of doctors are recommending that for their patients.

All right. Switching gears because I've just got a few seconds left, and I'm just going to make a comment. If we have time, Dr. Kadlec and Dr. Fauci, you all can respond, but we keep waiting. I've been here now 9 years, which is not nearly as long as some of the members of this committee, and every year we hear that we're almost there. We're getting there. We hear—we see great slides, and you all do great work.

And Dr. Burgess said you are all some of his favorite people. I would agree with that. You all are doing great work, but you know, is this year going to be any different? Are we going to come back next year, and again, we still won't have something that's a non-egg-based vaccine?

Dr. FAUCI. We certainly are better off this year than we were last year in our quest for a universal flu vaccine. Last year we didn't even have a candidate.

This year, we're now 8 months in phase one, and by early 2020, we'll know clearly is it safe and does it induce the kind of response that you would predict would be protective. So clearly, there's a difference between the last time we spoke at the hearing.

Mr. GRIFFITH. Yes. And there's always advancement. I'm just looking for that day when there's—coming from a family with a lot egg-based vaccine problems because of the egg-based situation, I'm really looking forward to the day when we can say that we have more than 50 percent of the vaccine out there is non-egg-based.

I yield back, Madam Chair.

Ms. DEGETTE. I thank the gentleman. The gentleman missed the slide presentation, and so we will be——

Mr. GRIFFITH. No. I saw the slide presentation, or I would have had a much more biting question. But the presentation was great. I saw it. It was good.

Ms. DEGETTE. We'll get you a copy.

The Chair now recognizes the gentlelady from New York for 5 minutes.

Ms. CLARKE. Thank you, Madam Chair, and I thank our Ranking Member Guthrie for convening this very important hearing on the influenza virus and what can be done across the Federal Government to improve and protect public health as we near peak flu season here in the United States.

I want to thank our expert witnesses for being here today to testify on behalf of the CDC, NIH, HHS, and the FDA.

And while the national targets for vaccination rates for the past decade have ranged from 70 to 90 percent, depending on the population, it appears as though we are falling woefully short of these goals. Last season, only 43 percent of adults and 63 percent of children received their annual flu vaccine.

I'd like to better understand why these vaccination rates continue to be so low and what we can do to improve these numbers overall, also, specifically, what underserved populations. So Dr. Messonnier, what trend has CDC identified in recent years with regard to flu vaccination rates, and where are we making progress? Where are we falling short?

Dr. MESSONNIER. So I share your concern and your frustration that vaccination rates for influenza are lower than we want them to be. There has been a 5 to 8 percent increase in coverage from one year to the next, so the recent trends are optimistic, but history has shown us that, you know, that may not hold true.

And I think, as you've said, we have studied this issue. When we survey people to ask why they don't get the flu vaccine, what they say is that they don't think it works, they're concerned that it's not safe, and "Oh, well, flu isn't that serious."

We definitely also know that we see lower vaccination coverage rates in rural areas, in people of lower socioeconomic status, and the data really does indicate that, especially when people aren't convinced of the value of a flu vaccine, how easy it is to get the vaccine matters.

Ms. CLARKE. Are there particular populations who face barriers to accessing the flu vaccine, resulting in coverage disparities?

Dr. MESSONNIER. I think that our data suggest people of lower socioeconomic status, people without health insurance, people in rural areas, this is data in children, have lower vaccination rates. I'm especially concerned with the issue for children because the vaccines for children's program provides a safety net for children who can't afford vaccines. Those children should be able to get vaccines easily, and yet vaccination coverage for children is still unacceptably low.

Ms. CLARKE. Dr. Marks, you've already attested to the safety of the flu vaccine. Unlike other vaccines, however, the flu vaccine is recommended every season over the course of a person's life. What can you tell us about the studies that have looked into the long-

term effects of the flu vaccine to calm concerns people may have? And I know you've said some of it already here today, but I think it's worth reiterating.

Dr. MARKS. Thanks very much for that question.

So both for childhood vaccines and for adult vaccines, there have been numerous studies that have looked at the vaccination schedules and at repeated vaccination, and FDA continues to use its large database surveillance systems to look at the safety of vaccines. All indications are that the current vaccine regimens are safe and effective for their—in their intended schedules, and there's really no reason not to get vaccinated routinely and that the benefits greatly outweigh any risks.

Any medical intervention has small risks, but vaccines are among the most amazing health interventions of the 20th century and of the 21st century, that is, in terms of being public health interventions that have reduced illness and prevented deaths.

Ms. CLARKE. And, Dr. Fauci, according to your testimony, over the last 15 years, the effectiveness of seasonal influenza vaccines have ranged from 10 to 60 percent. Why does NIH, along with your fellow public health agencies, still recommend the flu vaccine each season?

Dr. FAUCI. Thank you for that question, and it's really an important question. When you talk about effectiveness, you've got to understand that, even if a vaccine is not effective in preventing infection, it can clearly mitigate the seriousness of the illness, prevent hospitalization, and certainly prevent death.

And that's the reason why you've heard all of us say, regardless of what the percent efficacy is on a chart, it is always better to get vaccinated than not to get vaccinated, because some degree of protection, either against infection or the complications of infection, are very important and advantageous. So many lives are saved—many, many lives—even with a vaccine that is not optimally protective.

Ms. CLARKE. Very well. It is clear that more needs to be done to increase the number of people who get vaccinated, particularly for those more vulnerable to the flu and marginalized from care.

And improving the vaccination rate will not only serve public health in the broad sense, it would also save lives. And I think there's an appointment at the attending physician with my name on it.

I yield back, Madam Chair.

Ms. DEGETTE. I thank the gentlelady.

I want to thank the witnesses for coming today. In case there's any mistake, the unified, bipartisan message from this hearing is: Get your flu shot. This week's a good time to do it because it's the flu shot week, and we don't know how bad this season's going to be, so everybody needs to get their flu shot.

It's hard to get such bipartisanship that we were up here saying the Members felt like we could all exchange opening statements and give each other's opening statements, and they would still have the same impact. So it's really important that people get their flu shots.

I want to remind Members that, pursuant to the committee rules, they have 10 business days to submit additional questions

for the record to be answered by witnesses who have appeared before the subcommittee. I ask the witnesses to respond promptly to any such questions should you receive any, and with that, the subcommittee is adjourned.

[Whereupon, at 12:14 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

CDC Report: Investigation of Respiratory Illness in U.S. Border Patrol Facilities, December 2018—January 2019

Background

At the request of the U.S. Department of Homeland Security (DHS), following reports of respiratory illness among persons migrating across the U.S.-Mexico border, three CDC teams visited DHS Border Patrol facilities in December 2018 and January 2019 to assess and make recommendations for infectious disease surveillance and reduction of disease transmission, with special focus on respiratory diseases (particularly influenza).

Increased respiratory illness is expected during influenza season, which typically occurs between October and May in the Northern Hemisphere. Influenza activity typically peaks in the United States during January or February. Transmission of influenza and other respiratory viruses can be enhanced in crowded settings. While individuals seen in border patrol facilities are intended to be present only for short periods of time (generally ≤72 hours), processing of persons passing through these facilities may be slower during some periods, fostering increased crowding that may enhance likelihood of respiratory disease transmission.

The first CDC team visited border facilities in the El Paso and Yuma sectors on December 29-30, 2018. El Paso sector sites were the Paso Del Norte (PDT) Central Intake Station, El Paso Station 1 (Station 1), and Clint Station. Yuma sector sites were the Yuma Processing Center and the Wellton Border Station. During this period, El Paso and Yuma facilities were over capacity due to increasing numbers of family units crossing the border and prolonged length of stay (up to eight days). This team made initial recommendations for infection control practices and respiratory illness monitoring in these facilities.

The second and third CDC teams visited the El Paso Sector facilities from January 2-11 2019. The included facilities were Paso Del Norte (PDT, the central intake facility for apprehended migrants), El Paso Station 1 (Station 1, which houses family units), and Clint Station (which houses unaccompanied children [UAC] only). Team 2 conducted enhanced respiratory illness surveillance to characterize respiratory agents circulating among persons crossing the border into the El Paso Sector. Team 3 assessed the feasibility of implementing influenza antiviral treatment and influenza vaccination in these facilities.

This report focuses specifically on observations, surveillance, and recommendations related to influenza.

Summary of Border State Influenza Activity

Since December, 2018 through January, 2019, the percent of respiratory specimens positive for influenza has been elevated in clinical laboratories along the US Mexico border which participate in national Surveillance (Figure 1). Most of the characterized influenza specimens at the state Public

Health laboratories are influenza A(H1N1)pdm09 viruses (Figure 2). These trends are similar to national trends (https://www.cdc.gov/flu/weekly/index.htm).

Summary of CDC Enhanced Influenza Surveillance at El Paso Sector Border Patrol Facilities, January 6-11, 2019

Methods

Enhanced respiratory illness surveillance was initiated on 6 Jan 2019 thru 11 Jan 2019 at PDT, Station 1, and the Clint Facility, among migrants apprehended daily by Border Patrol Agents. Individuals who indicated that they were ill at their initial intake and all children <18 years of age were medically evaluated and were screened to determine if they met the case definition for acute respiratory illness, defined as presence of any one of the following: fever (≥38° C), subjective fever (feverishness, chills), cough, runny nose, or nasal congestion. Individuals meeting this case definition were asked to participate in the enhanced surveillance. A short questionnaire and three specimens were collected (one oropharyngeal swab and one mid-turbinate nasal swab for a respiratory panel) and one mid-turbinate nasal swab for the influenza rapid diagnostic test.

Results

A total of 65 persons were tested, 6 of whom were positive for influenza by rt-PCR (Table 1). All were identified as influenza A(H1N1)pdm09. All influenza-positive persons were males; 3 were in PDT and 3 in Station 1. There were no positive influenza virus detections among UAC tested at the Clint facility. There was no clustering of positive detections by age group or country of origin.

The team piloted the use of the Sofia2 rapid influenza diagnostic kit in the field. Only four of the five influenza positive detections using the Sofia2 kit were positive for influenza by rt-PCR; an additional two individuals with rt-PCR positive influenza were not detected using the Sofia2. Two influenza A(H1N1)pdm09 viruses were confirmed to be susceptible to neuraminidase inhibitor drugs by neuraminidase activity detection assay.

Summary of Observations by CDC Teams

1. **With inadequate DHS medical infrastructure, illness in the border patrol facilities stresses both the border patrol staff and the community medical infrastructure.**

- Border patrol agents must accompany each ill person to the emergency room, which reduces staff available in the facility and patrolling the border.
- Border patrol agents do not have training to triage or identify acutely ill migrants.
- Migrants may have additional medical needs because of stress and exposures during of the journey, which may cause increased risk of illness. They may also be less likely to request medical care because of communication barriers and their vulnerable migrant status.

- During influenza season, local emergency rooms are often at capacity taking care of acutely ill persons, and may be unable to absorb an increased number of migrants being taken to theemergency room for evaluation.

2. **The number of individuals in each of these facilities and the duration of their stay, is dynamic and difficult to anticipate, posing unique challenges to implementing control measures.**
- The number of individuals in custody at the three surveillance facilities varies throughout the day as migrants are moved between facilities and may not align with overall apprehension numbers. The number at the facilities changes throughout the day. Specifically, most of the migrants have their intake with Border Patrol Agents at the PDT Facility. After the migrants go through intake, they are transitioned into holding cells while they wait to be transferred to another facility for further processing.
- The movement of individuals from PDT to these other facilities is variable and depends on the capacity and the occupancy levels at those facilities. Migrants can be moved to one of the other facilities in the El Paso Section (11 facilities total), but family units are primarily sent to Station 1, UACs are primarily sent to the Clint Facility, and prosecutable males or females are sent to Ysleta. After migrants finish the processing step, they are released from Border Patrol custody to Immigration and Customs Enforcement or are otherwise incarcerated.

3. **Border Patrol facilities are not set up to be shelters, but during times of high occupancy and longer stays, the environment may be similar to shelters.**
- While optimally persons entering border control facilities are there for a short time (ideally ≤72 hours), periodically transit through these facilities slows, leading to increased crowding.
- During these periods, potential for infectious disease transmission may increase, and the facility environment is similar to a shelter from an infection control standpoint. Thus, infection control measures and syndromic surveillance to minimize infectious disease outbreaks in shelters could be useful.
- Current infrastructure is not sufficient to assure rapid and adequate infection control measures, including limited isolation options and agent training.

Recommendations

The complete set of recommendations below is for use during the influenza season and can be used to plan for the next season. Recommendations CDC identifies as high-priority when planning include:

- Implement screening for respiratory symptoms of individuals
- Plan for appropriate space to isolate ill migrants
- Have a sustainable plan for medical triage by trained healthcare providers

- Ensure supply of face masks and hand sanitizer in the facilities
- Ensure staff are vaccinated prior to the influenza season
- Work with local public health department to develop an approach to reporting

These recommendations reflect observations discussed above, while acknowledging that circumstances in border facilities change. They focus primarily on prevention and control of influenza, and should be considered during influenza season and periods of decreased transit time (longer holding times) and/or increased census in the El Paso sector border control facilities. The basis of this guidance rests on the assumption that during such periods, influenza transmission risk is similar to that in shelter settings.

1. Ensure sustainable medical infrastructure during times of increased crowding

Based on CDC observations, temporary medical staff supporting these facilities has been very effective at providing appropriate medical triage and management of respiratory illness. Therefore, CDC recommends continuing this support. Additional resources may be needed during periods of increased crowding.

a. Establish/maintain sustainable infrastructure at the larger border patrol stations (ideally those with capacity ≥100 persons) to support medical screening, monitoring, prevention strategies and treatment of persons with uncomplicated illness.
   i. This infrastructure should ideally remain in place throughout the influenza season and as long as migrants are residing in border stations for >72 hours, particularly when facilities are over capacity and crowding is increased.
   ii. If unable to establish infrastructure at stations with capacity ≥100 persons, efforts should be made to sustain these services at stations with the highest immigration volume.

b. Routine collection of vital signs including temperature, respiratory rate, heart rate, blood pressure and oxygen saturation should be implemented during medical evaluations to identify/triage ill persons and detect severe illness including sepsis.

c. In addition to the intake screening, consider a daily walk-through of the holding facility by medical personnel who can identify potential ill persons that need further evaluation.

2. Infection Prevention Measures

a. Implement administrative controls to rapidly assess respiratory symptoms at intake and immediately separate (cohort) and/or mask symptomatic persons. Adding specific questions to identify respiratory and infectious symptoms to initial intake questionnaire (cough, chills, diarrhea, rash, etc.) will increase likelihood of identifying persons with illness.

b. Ensure availability of personal protective equipment for staff and ill migrants. Persons with respiratory symptoms should wear a facemask until they are able to be isolated.
c. Ensure adequate handwashing or hand sanitation is available.
d. Use simple health education and communication messaging around hand washing or hand sanitizer, use of facemasks, and awareness of respiratory symptoms for staff and migrants.
e. As feasible, reduce the time individuals are held at border stations.
f. Determine a feasible approach to isolate or cohort individuals and/or families with members with respiratory symptoms, including consideration of temporary structures to provide additional space for isolation and to keep family members together.

3. **Influenza Vaccination of Facility Staff**
   a. We recommend that all staff at all facilities who are not yet vaccinated this season and who have no contraindications to vaccination be offered an age-appropriate influenza vaccine according to current CDC/ACIP recommendations. Ideally, influenza vaccination should be offered to staff each season.

4. **Syndromic (Symptom-based) Surveillance**
   a. Conduct syndromic (symptom-based) surveillance to monitor prevalence of acute respiratory illness
      i. Screening evaluations should include specific questions to identify signs and symptoms (fever, chills, cough, etc.) to increase likelihood of identifying persons with acute respiratory illness.
      ii. Ongoing daily monitoring for new onset of acute respiratory illness signs and symptoms should be instituted after the initial screening, as long as migrants are residing within the border stations.
      iii. Develop a system to monitor data to establish baseline and flag changes in the proportion of evaluated persons with illness if feasible. This could be centralized or conducted at selected high-volume facilities.
   b. Monitor proportion of people in each facility that are taken to the emergency department or hospital for evaluation, and the reason for the visit. This information should be transmitted to the state health department.
   c. If not currently in place, electronic systems to capture syndromic surveillance and medical visit information would be preferable and enhance communication with DHS, health departments and ICE and ORR facilities.
   d. Recommend continuation of syndromic surveillance year-round, for respiratory illness as well as other infectious syndromes (e.g. gastrointestinal, rash, and neurologic).

5. **Surveillance and reporting to the state health department**
   a. Implement a mechanism for reporting to health departments information concerning migrants who are sent to emergency departments or healthcare providers outside the facility. This can range from a report on each case or a daily summary report, depending on the needs of the health department.

b. Implement a mechanism for assuring reportable diseases are reported to the state/local health department.

6. **Monitoring of ill migrants**
   a. Provide ongoing monitoring by medical personnel of the health of ill persons in the facilities (e.g., those noted to be ill on initial screening but not judged to need outside care, and those discharged from outside care back to the facility), so that further appropriate care can be provided for those whose condition deteriorates.
   b. Discharge information from hospital stays/ED visits should be provided back to on-site medical personnel (or other responsible trained DHS staff).
   c. Medical records of migrants should follow the individual as they progress to another facility or into the community.
   d. To facilitate control of communicable illnesses and prevent spread among different facilities, develop criteria to determine when ill persons may be transferred to the next facility or to ICE custody.

7. **Influenza Antiviral Treatment**
   Early antiviral treatment can shorten the duration of influenza-associated illness and may reduce the risk of complications from influenza, as well as reduce need for referrals to outside medical facilities. CDC recommends use of antivirals, as feasible, in facilities with medical infrastructure.
   a. Given current levels of influenza circulation and crowded conditions, empiric treatment with an approved influenza antiviral of all persons with acute respiratory illness suspected to be due to influenza is recommended as soon as possible within the week of illness onset, if this can be reliably discerned.
      a. Acute respiratory illness may be defined as
         i. fever or feverishness **and** cough for those ≥2 years old
         ii. fever or feverishness **or** cough or rhinorrhea or nasal congestion for those <2 years old
      b. This is consistent with CDC recommendations for facilities providing temporary or longer term group housing such as shelters for displaced persons experiencing influenza outbreaks.
   b. Through the end of the influenza season, clinical suspicion of influenza, without diagnostic confirmation, is sufficient to initiate antiviral treatment. Sources for influenza activity include Fluview and local/state health department communications.
   c. If crowding within facilities is alleviated and occurrence of respiratory illness in facilities has decreased, antiviral treatment decisions may be made using a narrower case definition of influenza-like illness based on clinical judgement or directed by the results of clinical influenza testing, in settings where available.
      a. For persons with suspected or confirmed influenza, antiviral treatment would then be recommended as early as possible for persons at high risk for influenza complications, including children <5 years (particularly those <2 years), adults ≥65 years, pregnant females, and those with certain chronic medical conditions.

8. Influenza Vaccination of Migrants

Influenza vaccination should be implemented at the earliest feasible point of entry to allow for maximum protection of migrant and potential to reduce transmission in Border Patrol Facilities.

a. Annual influenza vaccination for all persons ≥6 months of age is recommended (no influenza vaccines are licensed for children <6 months).
b. In facilities with medical infrastructure, all migrants present for sufficient time for vaccination who do not have contraindications should be offered an age-appropriate influenza vaccine.
    i. All migrants should be presumed unvaccinated unless records indicating vaccination are available.
    ii. For persons with moderate or severe acute illness, with or without fever, due to any cause, vaccination should be deferred until the acute illness has resolved.
c. Priority groups for vaccination include children aged 6 months through 18 years and pregnant women.
    i. All children 6 months to <9 years should receive the first dose of vaccine at the border patrol station and a second dose ≥4 weeks later.
d. Vaccination may be considered for adults >18 years of age if feasible.

9. Diagnostic Test-Based Surveillance

a. Given ongoing risk of influenza transmission, CDC recommends that the decision to treat with antivirals be based upon clinical suspicion for influenza, and should not be based upon diagnostic testing.
b. However, where feasible, in order to assess ongoing circulation of influenza viruses, periodic (e.g. once weekly or biweekly or monthly) diagnostic testing on a sample of symptomatic persons may be considered for surveillance purposes:
    i. Rapid diagnostics for influenza screening (using nasal swabs) to determine presence of influenza virus circulation among migrant population (note that rapid molecular influenza testing would be preferred over rapid antigen detection tests, if feasible).
    ii. In addition, or as an alternative, consider sending swabs collected from ill persons to a public health laboratory for influenza diagnosis, as well as antigenic and genetic characterization.

Additional considerations for influenza vaccine implementation:

- Influenza vaccination of migrants may be most feasible at the border stations with current existing medical infrastructure.
- Implement vaccination programs at border stations that will maximize contact with the greatest number of people.
- Local community partnerships should be explored to support vaccination efforts.
- Establish a working relationship with the Texas State Immunization Program (or other state health department) for technical assistance regarding issues related to vaccine supply, storage and handling requirements including maintenance of cold chain, and quality control measures.
- Vaccination records should follow migrants as they progress to other facilities or the community.
    - This may be accomplished through forming a relationship with the Texas State Immunization Information System (IIS) for stations inside the Texas borders, along with providing paper documentation.
- Identify personnel qualified to administer vaccines and establish training and documentation protocols and procedures for vaccine administration.
- Appropriate refrigeration units will need to be procured and monitored with temperature data loggers to provide for vaccination storage.
- Vaccine information should be provided to the all vaccine recipients ≥18 years of age and to guardians of those <18 years of age, in the recipient's primary language.

Table 1. Demographics of Individuals Surveyed

	All N=65		Influenza PCR/TAC Positive Infections* N=6		Non-Influenza Enrollees† N=59	
Demographics	**N**	**%**	**N**	**%**	**N**	**%**
Age, y, median (IQR)	16 (19)		16.5 (13)		16 (21)	
0-4	8	12.3	1	16.7	7	11.9
5-12	16	24.6	1	16.7	15	25.4
13-17	16	24.6	2	33.3	14	23.7
18-49	25	38.5	2	33.3	23	39.0
Sex						
Male	39	60.0	6	100.0	33	55.9
Female	26	40.0	0	0.0	26	44.1
Country of Origin						
El Salvador	8	12.3	0	0.0	8	13.6
Guatemala	38	58.5	3	50.0	35	59.3
Honduras	16	24.6	3	50.0	13	22.0
Mexico	3	4.6	0	0.0	3	5.1
Border Patrol Facility						
Central Intake Facility	41	63.1	3	50.0	38	64.4
Family Units Facility	18	27.7	3	50.0	15	25.4
Unaccompanied Minor Facility	6	9.2	0	0.0	6	10.2

*Among influenza positive samples, 6 identified as H1N1pdm09.
† 29 individuals had no viral agents identified by PCR or TAC. 23 had only 1 viral agent identified by PCR or TAC (Rhinovirus, Adenovirus Human Metapneumovirus, Human Coronavirus 3). 7 had 2 viral agents identified by PCR or TAC (Rhinovirus/Human Coronavirus 1, Rhinovirus/Parainfluenza Virus 1, Rhinovirus/Cytomegalovirus, Rhinovirus/Enterovirus, and 3 individuals with Rhinovirus/Human Coronavirus 3).

Figure 1

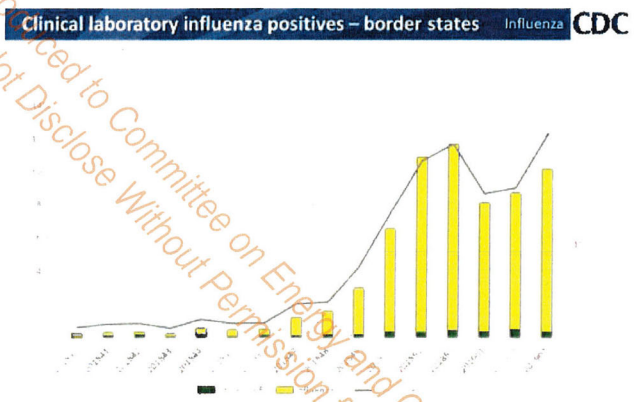
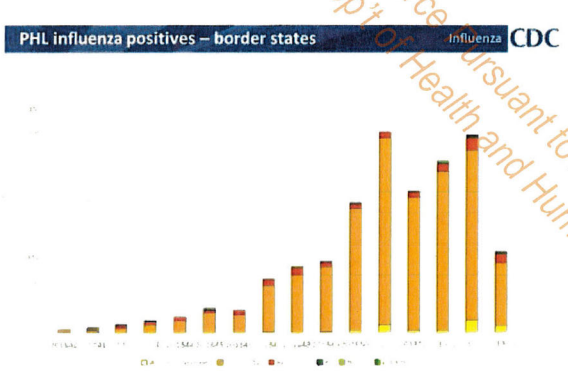


Figure 2:



Committee on Energy and Commerce
Subcommittee on Oversight and Investigations

Hearing on
"Flu Season: U.S. Public Health Preparedness and Response""

December 4, 2019

Dr. Nancy Messonnier, M.D. (CAPT, USPHS, RET), Director, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention

The Honorable Jan Schakowsky (D-IL)

1. Though a bout of the flu can be miserable for any person affected, in older adults the consequences can be far more severe and long lasting. Frail adults in nursing homes suffering from vaccine preventable illness often experience permanent loss of mobility, reduced independence or ability to engage in activities of daily living, and increased mortality.

   Please elaborate on the specific impact of seasonal influenza in long-term care settings. What can health care providers in long-term care settings or public health officials do to protect this particularly vulnerable population from the flu?

Response:

The Advisory Committee on Immunization Practices (ACIP) has recommended annual influenza vaccination for residents of long-term care facilities, regardless of age, since 1988. Annual influenza vaccination is currently recommended for all persons 6 months of age and older without contraindications for vaccination. Residents of nursing homes and other long-term care facilities are at increased risk for medical complications attributable to severe influenza and are therefore a priority for vaccination. Because of this, the Centers for Medicare & Medicaid Services requires that nursing homes offer their residents annual influenza vaccination as a condition of certification and assesses vaccination on their resident assessment instrument. Health care personnel (HCP) in long-term care facilities may have direct or indirect contact with older adults, people with disabilities, and people with chronic medical conditions receiving care. Research shows that during a confirmed influenza outbreak in a long-term care facility, up to one in three residents and one in four staff develop an influenza-like illness.[1] It is well established that preventing influenza among HCP can help reduce the spread of influenza in resident populations.

ACIP has recommended influenza vaccination specifically for HCP and those who live with or care for people at high risk for influenza-related complications. In addition, 14 medical and health professional organizations, including the American Academy of Family Physicians;

[1] https://academic.oup.com/ageing/article/39/3/299/41378

American College of Physicians, and AMDA - The Society for Post-Acute and Long-Term Care Medicine have published position statements that support influenza vaccination for HCP.

The ACIP recommendations for health care personnel are based on a body of research that documents measurable benefits of vaccination. Vaccination may reduce staff illness and absenteeism and influenza-related illness and hospitalization, especially among people at increased risk for severe influenza illness. Even when viruses in the influenza vaccine and circulating influenza viruses are not well matched, vaccinated individuals are more likely to experience fewer complications due to influenza than people who do not get vaccinated.

As in previous seasons, coverage in the 2018–19 season was lowest among HCP in long-term care settings (67.9%) compared to HCP working in hospital settings (95.2%) followed by those working in ambulatory care (79.8%). Highest vaccination coverage among HCP was achieved in workplaces where vaccination was required, actively promoted, and/or offered onsite for at least one day. CDC has a long-term care web-based toolkit (https://www.cdc.gov/flu/toolkit/long-term-care/index.htm), which provides access to resources, strategies, and educational materials for increasing influenza vaccination among HCP and reducing influenza-associated morbidity and mortality among patients in long-term care settings.

The Honorable Brett Guthrie (R-KY)

1. According to a November 14, 2019, USA Today article, doctors are recommending the Fluzone High-Dose flu vaccine or FLUAD, a regular flu vaccine with an adjuvant, an immune stimulant, over the standard-dose flu vaccine for the demographic most vulnerable to seasonal flu: people 65 and older.[2] In addition, in an October 28, 2019, article, the Boston Globe reported that seniors are requesting the high-dose flu shot, and that roughly two-thirds of older adults who get flu shots now get high-dose vaccines.[3]

   The CDC's Advisory Committee on Immunization Practices (ACIP) has not made a preferential recommendation for Fluzone or FLUAD over the standard-dose flu vaccine, however, even though the high-dose vaccine was approved by the FDA in 2009 and has been on the market for a decade.

   Given the widespread support in the medical community for the high-dose vaccine or adjuvanted flu vaccine over the standard dose vaccine, is there a risk that the Centers for Disease Control and Prevention's (CDC) ACIP is being too cautious by not issuing a preferential recommendation for certain flu vaccines for seniors, and thus conveying the impression that the standard dose vaccine efficacy data is equivalent to the efficacy data of the alternatives?

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[2] Adrianna Rodriguez, *A super-vaccine for the flu is being marketed to people 65 and older. Is it legit or a scam?*, USA TODAY (Nov. 14, 2019), *available at* https://www.usatoday.com/story/news/health/2019/11/14/flu-shot-doctors-recommend-fluzone-high-dose-fluad-65-older/4178418002/.

[3] Robert Weisman, *Seniors clamor for high-dose flu shot, but it's not always easy to find*, BOSTON GLOBE (Oct. 28, 2019), *available at* https://pressfrom.info/us/lifestyle/health-fitness/-344145-seniors-clamor-for-high-dose-flu-shot-but-it-s-not-always-easy-to-find.html.

Response

CDC completely agrees about the importance of ensuring that adults 65 years and older are protected against influenza given that older adults are at higher risk of serious influenza and influenza-related complications including pneumonia and hospitalization. We understand that a preferential recommendation would have significant impact on consumers, providers, and industry. However, a preferential recommendation requires consistent evidence of greater relative benefit of one vaccine over others. For influenza, the effectiveness of the vaccine is not consistent from season to season, and the relative effectiveness of one vaccine compared to another may also vary from season to season, which makes the evaluation of vaccines even more complex. Consideration of all relevant comparisons between vaccine types and consistent evidence of benefit across seasons is needed to inform a preferential recommendation, as well as a demonstration of favorable comparative safety profiles, acceptability, and feasibility.

In recent years, studies comparing different types of vaccines for older adults have been published. Relevant comparisons for which there are published data include studies of high-dose (Fluzone High-dose), adjuvanted (FLUAD), and recombinant (Flublok Quadrivalent) vaccines compared to standard-dose, unadjuvanted, egg-based inactivated influenza vaccines. While there is evidence of benefit for some vaccine types over unadjuvanted, standard-dose, egg-based inactivated vaccines for persons aged 65 and over (with the largest body of evidence being available for high-dose vaccine), these vaccines have not been compared against one another in randomized controlled trials or observational studies of laboratory-confirmed influenza associated outcomes. In addition, emerging evidence suggests further comparison of egg- vs. non-egg-based vaccines may be also important, particularly for H3N2 viruses, which cause severe illness in older adults. Even high-quality evidence from randomized controlled trials may not be generalizable across all seasons, potentially limiting the benefit of a preferential recommendation, and potentially increasing harm if a non-preferred vaccine is more effective in a given season.

Because we recognize the importance of this issue, CDC is working with other federal agencies to do additional studies and gather additional data that would assist with evaluation of these vaccines. In addition, our Advisory Committee on Immunization Practices (ACIP) is currently considering the available data and our current recommendations.

2. Individuals with the flu have an increased risk of bacterial infections, such as pneumonia. According to a new report published by CDC last month about antibiotic resistance threats, each year in the United States, more than 2.8 million people get antibiotic-resistance infections, and more than 35,000 people die as a result.[4] Given CDC's concerns and the devastating impact that antimicrobial resistance can have on individuals with the flu, what is CDC doing to address antimicrobial resistance?

Response:

[4] Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States* (2019), *available at* https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf.

Streptococcus pneumoniae (*S. pneumoniae*/pneumococcus) is the leading cause of bacterial pneumonia and meningitis in the United States. Influenza infections make people more vulnerable to pneumococcal pneumonia. Overall, there are more than 2 million pneumococcal infections each year in the United States, resulting in more than 6,000 deaths and an estimated $4 billion in total healthcare costs. In more than 30% of pneumococcal infections, the bacteria are resistant to one or more clinically relevant antibiotics.

Fortunately, the pneumococcal conjugate vaccine (PCV) effectively prevents S. pneumoniae infections, including antibiotic resistant infections. Since PCV was first introduced in 2000, it has reduced pneumococcal infections caused by the strains of pneumococcus in the vaccine, which have been the most resistant strains, by more than 90% in children, and it has reduced antibiotic resistant pneumococcal infections in children by 97%.

PCV also decreases the spread of antibiotic resistant *S. pneumoniae* strains to unvaccinated people because vaccinated people do not spread pneumococcus to others. Blocking the spread of these strains to unvaccinated people reduces resistant infections among the whole population, including adults. Since PCV introduction among United States children in 2000, the rates of antibiotic-resistant invasive pneumococcal infections caused by vaccine strains decreased by more than 60% among adults. Maintaining high vaccination coverage and encouraging appropriate antibiotic use will continue to slow the spread of pneumococcal resistance.

The Honorable Susan Brooks (R-IN)

1. During FDA's vaccine approval process, randomized clinical trials (RCTs) are essential to determining the safety and efficacy of a vaccine. However, after a vaccine becomes licensed, a tremendous amount of real-world evidence (RWE) is generated from the millions of Americans being vaccinated each season.

   Given the changing nature of the influenza virus, this data can show how vaccines behave and protect diverse and critical populations, such as children and the elderly, in "real" and across multiple influenza seasons. It allows researchers to better measure clinical outcomes and could be useful in guiding policies for FDA and CDC and improving vaccine technology in the future.

   In practice, RWE provides a living, breathing, pool of data to help the U.S. government and the global influenza community gain a practical perspective on how to predict and prevent the spread of influenza each season, and potentially determine best programs for vaccine implementation. But it appears the government and public health stakeholders are not taking advantage of these benefits and the data collected each year from vaccination programs run by CMS, the VA, and the DOD.

   a. What is CDC doing to capture more RWE during each flu season?

   CDC's influenza surveillance and vaccine effectiveness monitoring systems and studies provide foundational Real World Evidence (RWE) to inform public health and clinical

decision-making related to describing the real-time circulation of influenza viruses and advancing influenza vaccine improvements. CDC's U.S. Influenza (Flu) Vaccine Effectiveness (VE) Network and other VE evaluation platforms provide critical information for manufacturers and researchers in developing enhanced vaccines by collecting more specific data about how well the vaccine works each season.

Observational VE studies assess how influenza vaccines work by comparing the occurrence of influenza illness among people who have been vaccinated compared to people not vaccinated. VE is the percent reduction in the frequency of influenza illness among vaccinated people compared to people not vaccinated, usually with adjustment for factors (like presence of chronic medical conditions) that are related to both influenza illness and vaccination. CDC conducts several different studies of VE against different influenza outcomes each season to assess and confirm the value of influenza vaccination as a public health intervention against laboratory-confirmed influenza infections of different severities. Study results of VE can vary based on study design, outcome(s) measured, population studied, and the season in which the flu vaccine was studied. More information on the use of observational studies to evaluate VE, as well as the use of RCT's to evaluate the efficacy of vaccines can be found here: https://www.cdc.gov/flu/vaccines-work/effectivenessqa.htm.

Administrative data on medical care delivery and claims can also provide RWE related to how well vaccines are working. For example, CDC has worked with integrated healthcare and public health systems to combine data on medical care, clinical testing for influenza virus infection, and influenza vaccine status in order to assess VE in preventing influenza-associated hospitalizations among pregnant women and intensive care unit admissions among children. CDC has also partnered with the Centers for Medicare & Medicaid Services to compare the VE of standard versus enhanced influenza vaccines among older adults. However, findings from administrative data sources that lack laboratory confirmation of influenza infection must be interpreted with caution, as a patient's diagnosis with influenza may or not represent an actual influenza virus infection. These types of RWE complement the insights CDC gains from the US Flu VE Network and other prospective evaluations of VE.

b. What public health lessons could be learned from examining RWE every year?

Last year, CDC supported the initial expansion of its U.S. Flu VE Network to include more enrollees, add new immunity tests, and conduct special studies to evaluate VE in community settings and among high risk groups. However, in order to fully maximize CDC's ability to protect Americans from seasonal influenza, even more capacity is needed to conduct large scale studies of the variety of new vaccine products now licensed in the US. Investments in the CDC's VE studies are also needed to better understand some of the complex immune system dynamics that drive how different groups of people respond to influenza vaccine and infection. These activities could be supported with the proposed increase in the FY 2021 President's Budget.

CDC's domestic and global influenza surveillance systems provide the data that form the foundation of what we know about influenza – including when the season has started in the United States, what viruses are predominating and the nature and severity of associated disease. CDC's surveillance systems are not only important for public health and clinical guidance during the season, they also provide the scientific basis for vaccine virus selection. Further investments, such as the increase requested in the FY 2021 President's Budget, in influenza-data systems throughout the United States are needed to guide public and private sector decisions about new vaccine innovation and immunization recommendations. They must be modernized and enhanced to better track disease and viruses in near-real time, but also to obtain greater depth and precision of data.

c. Do you believe it would be useful to incorporate RWE into your decision-making processes during each flu season?

The Real World Data (RWD) and RWE generated by CDC play an important role in decision-making about influenza prevention and response, particularly related to influenza vaccine recommendations. As one example, data from CDC's U.S. Flu VE Network can inform the Advisory Committee for Immunization Practices' recommendations on influenza vaccine use. They are also important in informing yearly decision-making about vaccine composition and strain selection, and in communicating with healthcare practitioners and the public about the performance of influenza vaccines during the influenza season.

d. Could RWE be included in the future in FDA product labels?

This question related to FDA product labels is best directed to the FDA.

Committee on Energy and Commerce
Subcommittee on Oversight and Investigations

Hearing on
"Flu Season: U.S. Public Health Preparedness and Response""

December 4, 2019

Dr. Anthony S. Fauci, M.D., Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health

The Honorable Brett Guthrie (R-KY)

1. The National Institutes of Health's (NIH) written testimony states that the National Institute for Allergy and Infectious Diseases (NIAID) is supporting research to examine how the immune systems of young children respond over time to their initial influenza infection and their first vaccination.

   a. Is NIAID's research also examining how the immune systems of adults respond over time to influenza vaccinations?

   NIAID Response:
   NIAID is supporting research to examine how the immune systems of young children respond over time to their initial influenza infection and their first vaccination. These long-term cohort studies will help us better understand how repeat vaccinations and immune memory affect the ability to mount an immune response to different influenza subtypes. Humans encounter numerous influenza virus strains and vaccinations throughout their lifetime, with immune responses determined by the genetics of the virus, as well as by intrinsic host factors, such as genetics, age, health, and immune status. Recent data provide critical evidence that infection with influenza virus strains circulating during one's childhood elicits a lifelong immunologic imprint. The lifelong imprint then influences subsequent responses to novel strains or vaccinations, as well as helps the body mount an immune response against unfamiliar hemagglutinin (HA) subtypes from the same phylogenetic group as the original infecting virus. This phenomenon is termed "immunologic imprinting." While imprinting can induce protective immunological memory that may be helpful to combat influenza strains similar to the "imprint," some evidence suggests that imprinting may limit the generation of protective responses to novel influenza virus strains or vaccines that are considerably different from the original imprinting viruses.

   An improved understanding of how immunity develops and evolves over time in different age cohorts is one of the key scientific questions that NIAID identified in our 2018 *Strategic Plan for a Universal Influenza Vaccine*. The emergence of transformative new

technologies such as high-throughput sequencing and single-cell sorting provides the opportunity to better understand the fundamental basis for viral evolution and human immune repertoires. While the long-term studies discussed above will focus on children, the results could benefit people of all ages as researchers use the findings to investigate vaccine strategies that provide improved lifelong immunity against different strains of the influenza virus.

In addition, the NIAID-supported Human Immunology Project Consortium (HIPC) and Center for Human Immunology (CHI) are helping to evaluate different vaccine formulations and administration regimens, as well as identify markers of vaccine safety and effectiveness in different populations. HIPC scientists have identified molecular signatures that were predictive of influenza vaccine responses. Interestingly, these signatures appeared to be inversely correlated between younger and older individuals, suggesting that distinct mechanisms may be responsible for the lower response to influenza vaccination observed in older individuals. Findings from the HIPC and CHI studies could lead to the prediction of immune responses before vaccination and offer the possibility of modulating an individual's immune state before vaccination to improve the resulting antibody response.

NIAID-supported scientists in the Division of Intramural Research (DIR) and in the Centers of Excellence for Influenza Research and Surveillance (CEIRS) program are performing studies to help understand the adult immune response to influenza vaccinations over time. CEIRS scientists analyzed samples from a four-year study of serial annual influenza vaccinations in young adults and elderly adults. The researchers demonstrated that although younger individuals produced a better immune response after the first vaccination, age was less relevant after successive vaccinations. This finding suggests that the difference between the two age groups in their response to vaccination may be the result of the different vaccination and infection histories between these groups, in addition to the effect of an aging immune system.

NIAID recently launched the Collaborative Influenza Vaccine Innovation Centers (CIVICs) program, a new network of research centers that will work together in a coordinated, multidisciplinary effort to develop more durable, broadly protective and longer-lasting influenza vaccines. The CIVICs will focus on designing novel vaccine candidates and delivery platforms with an emphasis on cross-protective vaccine strategies that could be used in healthy adults as well as populations at high risk for the most serious outcomes of influenza, including children, older adults, and pregnant women. The CIVICs program also will conduct detailed immunologic analysis of samples collected from clinical trials of vaccine candidates and from human challenge studies. These analyses will help to define the immune responses required for broad and durable protective immunity and identify clear correlates of protection.

Collectively, these studies in children and adults are helping to improve our understanding of how the body responds to influenza infection or vaccination. This knowledge will inform our efforts to develop more broadly protective, or "universal"

influenza vaccines that could protect against a number of influenza strains over longer periods of time.

b. Do we have a good understanding on how repeat vaccinations affect the ability of adults to mount an immune response to different influenza subtypes?

NIAID Response:
NIAID is supporting research to better understand the role of repeat vaccination on the adult immune response to different influenza subtypes. Recently, NIAID-supported CEIRS investigators demonstrated that study participants receiving repeat influenza vaccinations exhibited a reduced ability to develop high-affinity antibodies to an important HA domain of all three influenza virus strains tested, regardless of the vaccine platform being used. Although the sample size of this study was small, the results suggest additional work is needed to determine whether repeat vaccination may contribute to lower vaccine effectiveness of seasonal influenza vaccines in humans.

NIAID-supported CEIRS investigators analyzed blood samples from a cohort of adults after the administration of seasonal influenza vaccine and observed that previously vaccinated individuals had lower post-vaccination levels of HA-specific antibodies against all influenza subtypes tested. The levels of two subtypes of T-cells known to play an important role in the antibody response to influenza vaccination and infection also were reduced after vaccination in the previously vaccinated group. However, some degree of protection was still afforded by the vaccine. These findings suggest that the dampening of the antibody response observed in repeat vaccine recipients may be related to diminished T-cell responses.

Although additional studies are needed to better understand the role of repeat vaccination in the development of immune responses to different influenza subtypes, it is important to note that seasonal vaccines remain the best way to prevent influenza virus infection. The CDC recommends that everyone six months of age and older should get an influenza vaccine every season with rare exception. Annual influenza vaccination is especially important for people in high-risk groups, such as seniors, pregnant women, and young children, as well as people who are in close contact with those at high risk.

The Honorable Jeff Duncan (R-SC)

1. You stated that "historically, the worst bioterrorist has been nature itself" referring to pandemic flu and in your March 14, 2019 testimony to the Senate Appropriations Committee, you testified that stockpiling flu vaccine is not yet possible because it changes from season to season and thus you have supported going "full speed ahead on the platform technologies." Combined with the government's stated goal of procuring a vaccine in 12 weeks:

   a. Do you support pursuing multi-modal platform technologies capable of responding not only to influenza but additional biological threats such as Ebola?

NIAID Response:
A critical component of preparedness is biomedical research to develop medical countermeasures that could be rapidly deployed in response to a naturally occurring or deliberately introduced infectious disease outbreak. This includes NIAID-supported research to develop multi-modal, or platform-based, technologies. Novel vaccine platforms that have been intensively studied employ recombinant DNA technology that bypasses the need to grow the virus. These platforms include recombinant proteins, viral vectors containing genes that express specific viral proteins, virus-like particles that can be manufactured, nanoparticles with high immunogenicity, and genetic approaches such as DNA and RNA that code for viral proteins. These platforms can be quickly modified for use against a variety of pathogens.

For example, NIAID scientists used newly identified Zika virus genetic information to rapidly develop a Zika vaccine candidate using a DNA vaccine platform that progressed from sequence selection to a first-in-human clinical trial in less than four months. The NIAID Zika vaccine candidate was developed with a readily deployable DNA vaccine platform that was previously used by NIAID to develop a West Nile virus experimental vaccine. Using this broadly applicable platform technology, NIAID was able to accelerate its response to a previously unrecognized public health threat. This particular platform, or a similar multi-modal technology, could be used to address other public health threats in the future.
NIAID will continue to support the development of multi-modal, or platform, technologies to enhance pandemic preparedness and response efforts.

b. How important is the speed with which we respond to a pandemic determine our ability to effectively combat it?

NIAID Response:
When novel influenza viruses have the capacity to spread efficiently among humans, the risk of a potential influenza pandemic is high. The speed with which we are able to respond to a potential pandemic is crucial to minimizing potential mortality and morbidity. Our best tool to prevent the next influenza pandemic is a safe and effective vaccine. Unfortunately, a vaccine likely would not be immediately available if a previously unidentified strain of pandemic influenza suddenly emerges, as has been the case in previous influenza pandemics.

Most existing influenza vaccines are produced by growing the virus in eggs. This is a time-honored, but time-consuming process. Currently, an updated – and sometimes a novel – influenza vaccine is needed for each new strain of influenza with pandemic potential. During the H1N1 influenza pandemic in 2009, a vaccine against the emergent virus strain was not available to the public until well after the peak of the pandemic had occurred. Continually "chasing" influenza viruses that jump from

animals to humans comes at a substantial economic cost and can leave public health at risk.

It is essential that we move beyond the current strain-specific influenza vaccine development strategy to get ahead of future outbreaks of pandemic influenza.

c. Do you think it's important to support pursuing multiple, novel technologies to ensure we can produce vaccines rapidly following a pandemic declaration?

NIAID Response:
NIAID has prioritized research to develop state-of-the-art vaccine platform technologies that could be used to develop universal influenza vaccines, as well as to improve the speed and agility of the influenza vaccine manufacturing process. These platform technologies include DNA, messenger RNA (mRNA), virus-like particles, vector-based, and self-assembling nanoparticle vaccines. NIAID-supported scientists are investigating an mRNA vaccine candidate that would allow for a more rapid and flexible response to both seasonal and pandemic influenza than do existing vaccine production strategies. NIAID's developments of vaccine platform technologies that significantly reduce the time to production for novel vaccines, including development of a universal influenza vaccine, are crucial to decreasing the response time in the event of a future pandemic.

Committee on Energy and Commerce
Subcommittee on Oversight and Investigations

Hearing on
"Flu Season: U.S. Public Health Preparedness and Response""

December 4, 2019

The Honorable Dr. Robert Kadlec, M.D. M.T.M&H, M.S., Assistant Secretary for Preparedness and Response, U.S. Department of Health and Human Services

The Honorable Brett Guthrie (R-KY)

1. One division within the U.S. Department of Health and Human Services (HHS) that did not testify at the December 4, 2019 hearing was the Centers for Medicare and Medicaid Services (CMS). CMS, however, can impact flu vaccination through its reimbursement policies.

   In order to improve both seasonal and pandemic influenza preparedness, should CMS consider preferential reimbursements—reimbursing certain products at a higher rate—to incentivize a greater domestic manufacturing footprint for different types of flu vaccines, such as the cell-based and recombinant vaccines?

   This question would be best addressed by the Centers for Medicare & Medicaid.

2. What steps is the Administration taking to address the pipeline of antibiotic drugs that are so critical for our pandemic response and national security?

Antibacterials are of specific concern as they relate to national security; if civilians are saved from an initial threat only to die from a subsequent hospital or community acquired bacterial infection, efforts to protect persons from public health threats have ultimately failed. Within the U.S. Department of Health and Human Services (HHS), the Office of the Assistant Secretary for Preparedness and Response (ASPR), Biomedical Advanced Research and Development Authority (BARDA) is using an integrated strategy to provide support across the medical countermeasure (MCM) development pipeline to support preparedness and response efforts focused on novel antibiotics.

BARDA seeks to revitalize the antibacterial pipeline through three primary efforts:

- **Combatting Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X): In partnership with the Wellcome Trust, the National Institutes of Health, the Bill and Melinda Gates Foundation, and the governments of the United Kingdom and Germany, BARDA supports the CARB-X program through a cooperative agreement awarded to Boston University since 2016 to support antibacterial innovation and early-stage research and development. The world's largest public-private partnership devoted to early-stage antibacterial development, CARB-X has**

provided over $174 million to support 54 projects. CARB-X's portfolio contains 33 active projects, including novel classes of antibiotics, new diagnostics, and nontraditional approaches. Six projects have advanced into the clinical trial phase, including a diagnostic program that recently transitioned into BARDA's advanced development portfolio.

- **Advanced Research & Development Portfolio: BARDA's advanced research and development portfolio currently supports 15 antibacterial candidates spanning 11 public-private partnerships. The candidates in the portfolio collectively address all five priority biothreats (Plague, Tularemia, Melioidosis, Glanders and Anthrax) and a majority of CDC's priority antibiotic threats. Seven of these candidates are currently being evaluated in Phase 3 clinical trials. BARDA supported research and development that provided part of the predicate for FDA approvals of Melinta's VABOMERE® (2017), Achaogen's (now, Cipla's) ZEMDRI™ (2018), and Tetraphase's XERAVA™ (2018). BARDA also supports a complementary next generation diagnostics development program. Future priorities focus on expanding the portfolio to include nontraditional approaches (e.g., bacteriophage, host-directed therapies, etc.) and vaccines.**

- **Project BioShield: Recognizing the importance of making next-generation antibiotics that overcome antibiotic resistance available in the SNS, BARDA entered into a partnership with Paratek Pharmaceuticals to support the continued advanced development, potential approval, and potential procurement of Nuzyra® (omadacycline) for the treatment of anthrax. Antibiotics like Nuzyra® that could address specific biothreat indications as well as multidrug resistance while at the same time broaden the SNS's current stockpile of antibiotics will dramatically enhance the nation's preparedness.**

The Honorable Jeff Duncan (R-SC)

1. In your March 14, 2019 testimony to the Senate Appropriations Committee, you stated "I think if you ever had a chance to look at the curves of, not necessarily what happened in 1918, but if we projected what would happen today in terms of the speed of the transmission of a flu-like illness in a population that's vulnerable, it would be explosive. And in some ways, the faster you can get vaccines, literally, saves thousands of lives. And again, the economic benefits are also derived from that." You stated that "One of the challenges we have now quite frankly with our flu vaccine supply is the predominance of that is from eggs."

    a. Given the issues associated with derivation of vaccines from eggs, both in time and efficacy, do you support investment in late-stage non-egg-based technologies?

In an influenza pandemic, the best protection is a vaccine that 'matches' the circulating pandemic virus. Production of vaccine in chicken eggs requires adaptation that can result in divergence of the vaccine from the circulating virus infecting humans, potentially reducing its effectiveness. Influenza vaccine produced with more modern technologies,

including cell-based and recombinant vaccines that do not require egg adaptation could result in a better "match" between the seasonal flu vaccine and the strains that are actually circulating. Further, egg-based production capacity cannot be readily increased in an emergency, because of the highly specialized facilities involved (and the requirement for hundreds of thousands of chicken eggs moving into the factory every single day). Vaccine produced by cell- and recombinant-based technologies utilize facilities that are more generic and common, potentially allowing expansion of production capacity and producing more vaccine faster, thereby enabling vaccination of more individuals sooner.

ASPR/BARDA has supported and continues to support investment in late-stage development and licensure of non-egg based seasonal and pre-pandemic influenza vaccine technologies.

Utilizing supplemental funds appropriated by Congress, ASPR/BARDA supported the development and production of 23 new or improved influenza vaccines, antiviral drugs, and diagnostics. Specifically, ASPR/BARDA began supporting the development of different cell-based manufacturing technologies in 2006. As a result of these investments, a cell-based influenza vaccine (Flucelvax®) was developed that can now be administered to individuals four years and older. Additionally, the first recombinant influenza vaccine (Flublok®) was developed for people over 18 years of age.

In addition to product development, ASPR/BARDA continues to support domestic manufacturing capacity for non-egg based influenza vaccines. Both of the new licensures noted above were accompanied by new U.S. manufacturing facilities/ capacity, adding to the single U.S. facility (for egg-based vaccine) that had operated previously and substantially increasing overall U.S.-based influenza vaccine manufacturing capacity. Most recently, in December of 2019, BARDA awarded a contract to Sanofi Pasteur to expand domestic manufacturing capacity for the recombinant influenza vaccine. This is in direct support of the 2019 Executive Order on Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health and will increase domestic capacity for both seasonal and pre-pandemic vaccine.

The overall capacity for influenza vaccine production in the U.S. is still predominantly egg-based; therefore, it is important to continue investments in the further optimization and expansion of non-egg based technologies to reduce overall reliance on egg-based products. Such efforts include the need to explore additional vaccine production platforms like fully synthetic production methods to further improve domestic vaccine response capabilities.

b. Do you believe HHS, specifically BARDA, should ensure novel, multi-modal technologies are being supported to better respond to influenza?

Yes; ASPR/BARDA has supported and continues to support development of new technologies that can be used to improve the response to influenza. Incorporation and development of new technologies to improve influenza response is done across all aspects of the response – from production, delivery and administration of vaccines, to improved diagnostics, personal protective devices, and therapeutics. Some specific examples include:

- **Cellular and Recombinant Vaccine Technologies**
- **Platforms that allow even faster vaccine production**
- **Adjuvants that can improve efficacy**
- **Alternative approaches to vaccine delivery that can increase coverage, effectiveness, and ease of administration**
- **Development of improved influenza antivirals and immunotherapeutics**
- **In-home, and eventually wearable, diagnostics**

c. Is there a benefit to our population to invest in platform technology that cannot only respond rapidly to influenza, but Ebola and other emerging threats?

Yes, there is significant benefit to national preparedness to support platform technologies that are adaptable and versatile to support an enhanced response. The availability of such platform-based approaches would transform national preparedness against currently known threats as well as newly emerging threats in the future. ASPR/BARDA is investing in multi-purpose, flexible manufacturing platforms to support multiple production requirements. While many of these approaches, particularly those that will be useful for an influenza response, are early in development, ASPR/BARDA has made and continues to make investments to accelerate development of platform-based vaccine technologies. For example, as part of the investment with the Zika supplemental funding, ASPR/BARDA funded development of a Zika vaccine made using mRNA technology. This technology has promise as a rapid platform for a number of infectious diseases, including influenza and novel diseases that may emerge in the future. This technology is already showing dividends, having progressed a candidate into clinical trials, providing data that will inform development of other vaccines, and identifying areas for process improvement that will benefit manufacturing of any vaccine utilizing this platform.

The Honorable Susan Brooks (R-IN)

1. Pandemic influenza and emerging infectious diseases are one of the greatest biological threats we are facing – but one thing I am aware of are the significant funding pressures on the entire Public Health Emergency Medical Countermeasure Enterprise (PHEMCE), especially the strategic national stockpile (SNS).

   The PHEMCE Multi-Year Budget outlined $1.2 billion in funds needed for the SNS in FY20. These funds are needed for replenishment of existing countermeasures and procurement of new products. And last year, I believe the FDA approved 28 new medical countermeasures & more were approved this year. The House Labor-HHS bill got as close to the needed number as possible - $920 million.

a. Could you explain how important adequate funding for the SNS is for ensuring we are prepared for the threats of pandemic influenza, emerging infectious diseases like Zika and Ebola, and intentional biological threats like smallpox or anthrax?

The Strategic National Stockpile (SNS) manages and delivers life-saving MCMs during public health emergencies. It is the largest federally owned repository of pharmaceuticals, critical medical supplies, Federal Medical Stations, and medical equipment that is available for rapid delivery to support federal, state, and local response. SNS's MCMs are intended to help state and local health agencies replenish depleted supplies or support a response requiring specific products not readily available (e.g. an antidote to a specific biological or chemical agent). Ultimately, if a biological, chemical, radiological, or nuclear event occurred in the U.S. today, the SNS is the *only* Federal resource readily available to respond once state and local MCM supplies are depleted. In addition, some SNS MCMs are not commercially available because of small supplies and limited use (e.g. anthrax). U.S. pharmaceutical supply chains run on a just-in-time model, often containing no more than a 30-day supply of pharmaceuticals under normal conditions. As a result, commercially available products may not exist in necessary quantities or be positioned in ways that allow rapid distribution and use during public health emergencies. If/when shortages occur, assets in the SNS support the initial response. The SNS is critical to enhancing national preparedness and ensuring MCMs are available if and when needed during public health emergencies.

The funding in the Fiscal Year (FY) 2020 appropriation will allow the SNS to make additional investments in key Public Health Emergency Medical Countermeasures (PHEMCE) priorities. The SNS requires funding to maintain the current inventory as well as replenishing products originally purchased under Project BioShield (PBS).

b. And, could you explain what happens if the SNS does not receive funding? My understanding is that inadequate funding places stress on the larger PHEMCE – and especially other priority areas like the Special Reserve Fund, or funding to combat Pandemic Influenza, EIDs like Ebola or Zika, or antimicrobial resistance.

PBS funding is used for initial MCM procurement and rarely supports ongoing maintenance and replacement of the product after it is approved by the Food and Drug Administration (FDA). The PHEMCE SNS Annual Review process recommends the most risk-balanced and sustainable portfolio of holdings for the SNS and supports more effective decision making to both maintain current capabilities and absorb additional products.

2. As you know, in October the White House issued an Executive Order titled "Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health." The Executive Order looks at four critical areas: (1) the health and economic impact of a flu pandemic; (2) ensuring an "all of government approach" to preparedness; (3) improving existing vaccines and developing new technologies; and (4) manufacturing more effective vaccines faster.

The EO referenced a recent Council of Economic Advisors (CEA) report which found a severe pandemic could have $3.7 trillion in economic costs and would lead to the hospitalization of 4.3 million people. The EO recommended a range of government actions to improve the 80-year old egg-based technology used in today's vaccines and speed the vaccine manufacturing process.

We know that HHS lacks sufficient Congressional funding to achieve these goals. Last year, BARDA received just $270 million for pandemic flu preparedness, while the most recent PHEMCE multi-year budget outlined $775 million in funding needed this year alone to achieve basic preparedness.

Dr. Kadlec, we know that once a pandemic is identified, the U.S. government will immediately need $10-12 billion just to provide vaccines to protect the American people. That doesn't take into account all of the funding now to prepare and implement the Executive Order.

a. Do you agree we need to devote substantially more funding to pandemic preparedness?

As you are aware, influenza poses one of the greatest, fastest spreading and most costly (in terms of lives and economic costs) threats we face as a nation. As noted in the White House Council of Economic Advisers Study on Influenza, "in a pandemic year, depending on the transmission efficiency and virulence of the particular pandemic virus, the economic damage would range from $413 billion to $3.79 trillion. Fatalities in the most serious scenario would exceed half a million people in the United States. Millions more would be sick, with between approximately 670,000 to 4.3 million requiring hospitalization."[1] The more prepared the nation is for the next pandemic, the more lives saved and less economic impact.

ASPR/BARDA has made significant progress in supporting innovation and domestic preparedness over the last decade, supporting advanced research and development leading to FDA licensure of the first non-egg based influenza vaccines, cell-based Flucelvax®, and recombinant-based Flublok®. Equally as important are ASPR/BARDA's substantial investments in establishing, maintaining, and expanding domestic manufacturing of these vaccines, increasing overall pandemic influenza vaccine manufacturing capacity from approximately 60 million antigen doses to over 600 million within six months of the start of production.

Significant gaps in response capabilities still exist, including the time and person-to-person interactions needed to diagnose infection (delaying treatment and increasing the likelihood of person-to-person virus transmission), lack of FDA-approved therapeutics for individuals with severe influenza disease, domestic manufacturing capacity and supply chain control

[1] The Council of Economic Advisers. (2019), Mitigating the Impact of Pandemic Influenza through Vaccine Innovation, October 30, 2019, https://www.whitehouse.gov/wp-content/uploads/2019/09/Mitigating-the-Impact-of-Pandemic-Influenza-through-Vaccine-Innovation.pdf

(for vaccine, adjuvant, therapeutics, and ancillary supplies), and time to availability and subsequent administration of first vaccine dose. ASPR/BARDA will continue to make progress in addressing these existing gaps to ensure technologies are available to address both seasonal and pandemic influenza, as well as for sustaining the successes achieved to date. Currently existing domestic manufacturing facility capacity, critical to the Nation's response capabilities, will be maintained.

b. What are you doing to ensure BARDA, CDC and other HHS agencies have the resources they need to be prepared?

ASPR is working with other components of HHS and with OMB to explain our needs through the FY 2021 President's Budget.

c. Will we see additional funding requests to support the EO in the President's Budget in February?

ASPR is working with HHS and the White House Office of Management and Budget (OMB) to finalize the FY 2021 President's Budget. We anticipate the Budget will be released in early February. ASPR looks forward to providing more details on our FY 2021 request at that time.

3. We know that influenza viruses change over time, creating serious challenges for public health. As a New York Times article described earlier this year, flu viruses evolve constantly – they are "ruthless masters of disguise" when it comes to tricking our immune systems.

   The egg-based manufacturing process has been a mainstay of influenza vaccine production for more than 80 years. This process is well established and has made a significant contribution to public health. However, dependence on egg-based technology has significant limitations, including long supply times and the potential for virus mutations during the production process as the virus adapts to grow in the eggs.

   Cell- based vaccine manufacturing can address limitations of the egg-based process. This technology provides the ability to scale flu vaccine manufacturing with greater efficiency and avoids egg-adaptation, thereby providing a better "antigenic" match to circulating strains.

   a. What is ASPR and BARDA doing to optimize the use of cell-based manufacturing processes for flu vaccines?

Investments in modern influenza vaccine technologies have led to the licensure of new cell- and recombinant-based influenza vaccines by the FDA. Through this advancement we can expedite manufacturing, including influenza vaccines with adjuvants that can provide more vaccine with less vaccine antigen (antigen-sparing) and greater cross-protection against antigenically-different virus strains. For cell-based manufacturing, ASPR/BARDA supported efforts by the cell-based influenza vaccine manufacturer to improve the manufacturing process, resulting in a doubling of domestic vaccine production capacity for that vaccine.

b. How can the growth and expansion of cell-based vaccines technologies improve our ability to respond to a flu pandemic and protect the American people?

In an influenza pandemic, the best protection is a vaccine that 'matches' the circulating pandemic virus. Production of vaccine in chicken eggs requires adaptation that can result in divergence of the vaccine from the circulating virus infecting humans, potentially reducing its effectiveness. Influenza vaccine produced with more modern technologies, including cell-based and recombinant vaccines that do not require egg adaptation could result in a better "match" between the seasonal flu vaccine and the strains that are actually circulating. Further, egg-based production capacity cannot be readily increased in an emergency, because of the highly specialized facilities involved (and the requirement for hundreds of thousands of chicken eggs moving into the factory every single day). Vaccine produced by cell- and recombinant-based technologies utilize facilities that are more generic and common, potentially allowing expansion of production capacity and producing more vaccine faster, thereby enabling vaccination of more individuals sooner. ASPR will continue to invest in next-generation technologies, platforms, and manufacturing processes to further improve the scale, flexibility, efficiency, and speed of influenza vaccines, as well as in clinical studies to better understand potential benefits of existing vaccines. In addition, utilizing these flexible manufacturing technologies domestically improves our capability to rapidly produce other critical MCMs for other threats.

c. Does the government have plans to procure additional doses of cell-based vaccines through agencies such as the VA and the Department of Defense to support the growth and usage of these innovative technologies, especially as I understand there is some evidence that these vaccines could provide better protection for vulnerable veterans and the military that stands on the frontline of America's defense.

HHS is unaware of plans for procurement at VA and DoD. This question would be best addressed directly by those Departments. ASPR does work in close collaboration with partners, including VA and DoD, to share information on current MCM development and discuss potential stockpiling of products. Thus, VA and DoD have information on the availability of potential product and where product is currently in the developmental pipeline.

4. During FDA's vaccine approval process, randomized clinical trials (RCTs) are essential to determining the safety and efficacy of a vaccine. However, after a vaccine becomes licensed, a tremendous amount of real-world evidence (RWE) is generated from the millions of Americans being vaccinated each season.

   Given the changing nature of the influenza virus, this data can show how vaccines behave and protect diverse and critical populations, such as children and the elderly, in "real" and across multiple influenza seasons. It allows researchers to better measure clinical outcomes and could be useful in guiding policies for FDA and CDC and improving vaccine technology in the future

In practice, RWE provides a living, breathing, pool of data to help the U.S. government and the global influenza community gain a practical perspective on how to predict and prevent the spread of influenza each season, and potentially determine best programs for vaccine implementation. But it appears the government and public health stakeholders are not taking advantage of these benefits and the data collected each year from vaccination programs run by CMS, the VA, and the DOD.

a. What is FDA doing to capture more RWE during each flu season?

This question would be best addressed by FDA.

b. What public health lessons could be learned from examining RWE every year?

Please refer to FDA's response.

c. Do you believe it would be useful to incorporate RWE into your decision making processes during each flu season?

Please refer to FDA's response.

d. Could RWE be included in the future in FDA product labels?

Please refer to FDA's response.

5. The President's September Executive Order (EO) on flu vaccines directs agencies, including ASPR and BARDA, to 'advance the development of new, broadly protective vaccine candidates that provide more effective and longer lasting immunities.' However, the recent BARDA RFI posted on October 30 only requests information on manufacturing capacity for vaccines and adjuvants. Will there be additional BARDA opportunities that are intended to help with research and development for new, broadly protective vaccine candidates – particularly for technologies that may be in Phase I?

Yes, there are and will be other opportunities to support advanced research and development of vaccine candidates for influenza. ASPR/BARDA utilizes a number of different approaches to obtain information, as well as solicit proposals, for advanced development of vaccines, therapeutics, and diagnostics to detect, prevent, and treat influenza. In fact, ASPR/BARDA currently has an open Broad Agency Announcement soliciting proposals for products to develop and improve influenza response capabilities, including improved vaccines.

The Honorable Frank Pallone, Jr.
Chairman
Committee on Energy and Commerce
Washington, D.C. 20515-6115

Dear Chairman Pallone:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the December 4, 2019, hearing before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, entitled "Flu Season: U.S. Public Health Preparedness and Response." This letter is a response for the record to questions posed by the committee.

If you have further questions, please let us know.

Sincerely,

Karas Gross

Karas Gross
Associate Commissioner for
Legislative Affairs

cc: The Honorable Greg Walden, Ranking Member, Committee on Energy and Commerce

The Honorable Diana DeGette, Chair, Subcommittee on Oversight and Investigations

The Honorable Brett Guthrie, Ranking Member, Subcommittee on Oversight and Investigations

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
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The Honorable Brett Guthrie (R-KY)

1. **An Executive Order issued by President Trump on September 19, 2019 directs the U.S. Food and Drug Administration (FDA) as well as other agencies to accelerate the adoption of improved influenza vaccine technologies.[1] What actions does FDA plan to take to implement FDA's responsibilities under the Executive Order? Please also include information about the timeline for these actions.**

FDA, in collaboration with the scientific community and influenza vaccine manufacturers, is working to improve influenza vaccine manufacturing. Several efforts related to the Executive Order have been initiated and are ongoing, including the development of:

- alternative methods to prepare the reference reagents needed for determining vaccine potency,
- new methods to expedite the calibration of potency reagents,
- improved assays to determine potency of influenza vaccines, and
- higher yielding vaccine candidates.

Successful development and implementation of these methods and technologies could help compress the timeline for the production process and provide greater predictability.

In terms of timelines, we are currently actively working in these areas, have recently made notable progress regarding improving the yield of a pandemic vaccine candidate, and expect the work on potency reagents to be ready for potential adoption into the commercial manufacturing process within the next three to five years, dependent upon their acceptance by the vaccine manufacturers.

In addition, the following are part of FDA's routine activities:

- FDA has been and is committed to continuing to work with its Federal partners, the scientific community, and vaccine manufacturers to help address the public health threat caused by seasonal and pandemic influenza.
- FDA has utilized in the past, and will continue to utilize, applicable regulatory pathways and programs to expedite development and evaluation of additional influenza vaccines.
- All influenza vaccines approved by FDA have been demonstrated to be safe and effective. It is critical that Americans know that they can rely on the safety and effectiveness of vaccines.
- FDA is facilitating the development and adoption of advanced manufacturing technologies for influenza vaccines, which have the potential to address the need for maximally efficient, agile, and flexible manufacture of both current and next-generation influenza vaccines.

[1] Executive Order, *Executive Order on Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health* (Sept. 19, 2019), available at *https://www.whitehouse.gov/presidential-actions/executive-order-modernizing-influenza-vaccines-united-states-promote-national-security-public-health/.*

2. A few years ago, we had a flu season where there was a bad mismatch between the flu vaccine and a flu strain that had drifted. If FDA were confronted with vaccine mismatch again, what would FDA do differently than in the 2014-2015 flu mismatch season to respond to the mismatch?

The process for making recommendations about which vaccine strains to include for each year's influenza season must occur many months in advance of influenza season. This is to accommodate the time that is 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.

With respect to the 2014-2015 influenza season, the drifted H3N2 viruses that were detected in the United States in March 2014 were uncommon. When a drifted virus first emerges, it is difficult to predict whether the virus will die out or circulate widely, or when either of those scenarios would occur. Leading up to the 2014-2015 influenza season, the drifted H3N2 viruses became more common after the WHO convened a meeting in September 2014 to select the seasonal influenza vaccine for the Southern Hemisphere. 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.

However, since then, FDA has proactively initiated several efforts to 1) improve communication about antigenically drifted influenza strains by periodic review with CDC of virus surveillance data for potential antigenic drift, 2) improve and expedite candidate vaccine virus availability by generating additional candidate vaccine viruses for drifted strains of concern, 3) expedite vaccine reagent preparation for drifted virus strains, and 4) improve vaccine testing methods by developing alternative potency assays with improved accuracy and sensitivity that could potentially expedite influenza vaccine availability. These efforts will help us to be more prepared to expeditiously respond to flu strain drifts in the future.

3. Under what circumstances would it be appropriate to pursue a monovalent rescue vaccine to respond to a drifted influenza strain?

The decision to pursue a monovalent influenza vaccine as an addition to a seasonal influenza vaccine already produced or in production would depend on a balancing of several factors:

- when during the influenza season the emerging influenza strain was detected,
- the probability that the strain was likely to emerge as a major threat to public health
- its potential public health impact based on its potential to cause morbidity and mortality,
- the ability to rapidly produce a matched vaccine candidate and the needed testing reagents, and
- the availability of adequate manufacturing capacity.

Balancing these factors is critical, because a decision to produce monovalent vaccine while seasonal vaccine production is still in progress could disrupt the production of the latter, potentially negatively impacting the overall influenza vaccine supply.

Discussions pertaining to pursuit of a monovalent rescue vaccine for the United States would include BARDA, CDC, FDA, and vaccine manufacturers. FDA and its Federal partners have already conducted an exercise regarding the potential production and release timelines for such a licensed vaccine.

The Honorable Jeff Duncan (R-SC)

1. **It appears that universal flu vaccines carry tremendous potential, as we do not need to modify the flu vaccine to a different strain each year. I also find it encouraging to hear there is tremendous progress with respect to universal flu vaccine development.**

   a. **How will the FDA treat regulatory approval of these novel vaccines?**

   For the past several years, FDA has been working to anticipate and address challenges associated with using new technologies in the development and approval of vaccines to prevent influenza disease. Evaluation of new influenza vaccine candidates is based on existing knowledge and experience with regard to currently licensed influenza vaccines, as well as state-of-the-art science. FDA has approved novel influenza vaccines, including cell-based and adjuvanted influenza vaccines, utilizing existing regulatory pathways and expedited programs, which would also be applicable to a universal influenza vaccine.

   b. **Is the FDA ready and prepared with an approach to consider these vaccine candidates for regulatory approval?**

   Yes, FDA is prepared. Please see above response. Furthermore, FDA is working with industry and HHS partners to facilitate the testing of candidate universal influenza virus vaccines, and to identify approaches to demonstrate the safety and effectiveness of universal influenza vaccines.

The Honorable Susan Brooks (R-IN)

1. **During FDA's vaccine approval process, randomized clinical trials (RCTs) are essential to determining the safety and efficacy of a vaccine. However, after a vaccine becomes licensed, a tremendous amount of real-world evidence (RWE) is generated from the millions of Americans being vaccinated each season.**

   Given the changing nature of the influenza virus, this data can show how vaccines behave and protect diverse and critical populations, such as children and the elderly, in "real" and across multiple influenza seasons. It allows researchers to better measure clinical outcomes and could be useful in guiding policies for FDA and CDC and improving vaccine technology in the future

   In practice, RWE provides a living, breathing, pool of data to help the U.S. government and the global influenza community gain a practical perspective on how to predict and

prevent the spread of influenza each season, and potentially determine best programs for vaccine implementation. But it appears the government and public health stakeholders are not taking advantage of these benefits and the data collected each year from vaccination programs run by CMS, the VA, and the DOD.

a. What is CDC doing to capture more RWE during each flu season?

Please refer to the Centers for Disease Control and Prevention's (CDC) response.

b. What public health lessons could be learned from examining RWE every year?

Please refer to CDC's response.

c. Do you believe it would be useful to incorporate RWE into your decision making processes during each flu season?

Please refer to CDC's response.

d. Could RWE be included in the future in FDA product labels?

FDA's Center for Biologics Evaluation and Research (CBER) acknowledges that RWE has the potential to be an effective approach to enhance vaccine clinical development, clinical science, and programmatic recommendations. CBER is therefore considering the use of RWE in regulatory decision making and to potentially support changes in labeling for licensed vaccines, provided that RWE studies are of adequate design and conduct.

For influenza vaccines, FDA is using large databases in the post-market setting to evaluate vaccine effectiveness. FDA has helped validate this methodology with data obtained in collaboration with the Centers for Medicare & Medicaid Services using their large database to compare the effectiveness of high dose versus standard dose seasonal influenza vaccines for people 65 years of age and older. This collaboration has provided valuable analysis in support of public health for these specific influenza vaccines.

2. **During FDA's vaccine approval process, randomized clinical trials (RCTs) are essential to determining the safety and efficacy of a vaccine. However, after a vaccine becomes licensed, a tremendous amount of real-world evidence (RWE) is generated from the millions of Americans being vaccinated each season.**

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prevent the spread of influenza each season, and potentially determine best programs for vaccine implementation. But it appears the government and public health stakeholders are not taking advantage of these benefits and the data collected each year from vaccination programs run by CMS, the VA, and the DOD.

a. What is FDA doing to capture more RWE during each flu season?

For influenza vaccines, FDA is using large databases in the post-market setting to further evaluate the effectiveness of FDA-approved vaccines. FDA has helped validate this methodology with data obtained in collaboration with the Centers for Medicare & Medicaid Services using their large database to compare the effectiveness of high dose versus standard dose seasonal influenza vaccines for people 65 years of age and older. This collaboration has provided valuable analysis in support of public health for these specific influenza vaccines.

b. What public health lessons could be learned from examining RWE every year?

At a minimum, FDA can review RWE each year for signs of an increase in certain adverse events or the occurrence of previously unseen events. For example, in the past FDA has used RWE to assess whether there has been any increase in Guillain-Barré syndrome with the seasonal influenza vaccine.

c. Do you believe it would be useful to incorporate RWE into your decision making processes during each flu season?

CBER acknowledges that RWE has the potential to be an effective approach to enhance vaccine clinical development, clinical science, and programmatic recommendations. CBER is therefore considering the use of RWE in regulatory decision making and to potentially support changes in labeling for licensed vaccines, provided the RWE studies are of adequate design and conduct.

d. Could RWE be included in the future in FDA product labels?

FDA is willing to consider the submission of RWE by sponsors for inclusion into product labels, and will assess each request upon its own merits. As stated above, CBER acknowledges that RWE has the potential to be an effective approach to enhance vaccine clinical development, clinical science, and programmatic recommendations. CBER is therefore considering the use of RWE in regulatory decision making and to potentially support changes in labeling for licensed vaccines, provided the RWE studies are of adequate design and conduct.

For influenza vaccines, FDA is using large databases in the post-market setting to further evaluate the effectiveness of FDA-approved vaccines. FDA has helped validate this methodology with data obtained in collaboration with the Centers for Medicare & Medicaid Services using their large database to compare the effectiveness of high dose versus standard dose seasonal influenza vaccines for people 65 years of age and older.

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