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

November 17, 2015

TO: Members, Subcommittee on Oversight and Investigations

FROM: Committee Majority Staff

RE: Hearing on "U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?"

The Subcommittee on Oversight and Investigations will hold a hearing on Thursday, November 19, 2015, at 10:00 a.m. in 2322 Rayburn House Office Building, entitled "U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?" This hearing follows up on the Subcommittee's hearing on February 3, 2015, that examined the U.S. public health response to seasonal influenza. The Subcommittee will be examining the lessons learned from last season's influenza vaccine mismatch to the predominant influenza virus that resulted in more deaths and hospitalizations because of the vaccine's lower than usual effectiveness. The purpose of the hearing is to better understand the key challenges in flu vaccine development that the U.S. public health agencies seek to address and review recommended actions to improve seasonal influenza preparedness.

I. WITNESSES

Dr. Anne Schuchat
Principal Deputy Director
Centers for Disease Control and Prevention (CDC)

- *Makes recommendations on who should be vaccinated, tracks the spread of influenza and vaccination rates, and disseminates public health messages encouraging vaccination and other protective measures, such as hand-washing.*

Dr. Karen Midthun
Director, Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

- *Selects the influenza strains to include in the annual influenza vaccines and for licensing vaccines.*

Dr. Robin Robinson
Director
Biomedical Advanced Research and Development Authority (BARDA)
Office of the Assistant Secretary for Preparedness and Response

- *Funds the research and development of influenza vaccines.*

Dr. Carole Heilman
Director
National Institute of Allergy and Infectious Diseases (NIAID)

Division of Microbiology and Infectious Diseases
National Institutes of Health (NIH)

- *Conducts and supports research on influenza.*

II. BACKGROUND

A. The Influenza Threat

Influenza is a leading cause of death in the U.S. Influenza is a contagious respiratory illness caused by varying virus strains and can range in severity from mild to lethal. In both its seasonal and pandemic forms, influenza is an ongoing public health concern.[1] In the northern hemisphere, seasonal influenza may begin as early as August and generally diminishes by April. An average of 62 million Americans —about 20 percent of the U.S. population —get the flu each year.

Influenza is considered one of the leading causes of death in the U.S., especially in a severe season. Based on 2010 data, CDC has estimated that the number of deaths annually caused by influenza and pneumonia was 53,826. [2]

According to CDC estimates for the 1976-2006 time period, seasonal influenza has been associated with as few as 3,000 and up to almost 50,000 deaths each year in the U.S. On average each year, more than 36,000 individuals die and an estimated 226,000 are hospitalized from influenza and related complications.[3] A study published in 2007 estimated that more than $10 billion is spent annually in direct medical costs for hospitalizations and outpatient visits from seasonal influenza-related complications[4] and there is an overall annual economic burden of $87.1 billion.[5]

Detailed published estimates of influenza-attributable deaths by age, type, and subtype have not been updated by the CDC for seasons beyond the 2006-2007 influenza season.[6] CDC does not know exactly how many people die from seasonal flu each year. The reasons for this include: states are not required to report individual seasonal flu cases or deaths of people older than 18 years of age to CDC; many influenza-related deaths, such as from pneumonia, may not include any mention of influenza on the death certificate; many patients (especially the elderly)

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[1] Seasonal flu is an outbreak that follows predicable seasonal patterns. Pandemic flu is a worldwide outbreak of a new form of flu virus, which can spread easily from person to person because they have no immunity.

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

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

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

[5] N.A. Molinari, et al., 25 Vaccine 5086 (2007).

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

may die from pneumonia unrelated to influenza, so figuring out which cases to include in an analysis can be difficult; most people who die from seasonal flu-related complications are not tested for flu or they seek medical care when flu can no longer be detected.

Given the difficulties on getting exact numbers of flu-related deaths, researchers have turned to a variety of modeling techniques to estimate deaths. One retrospective database analysis, which estimated influenza deaths in the U.S. by analyzing data for 12 influenza seasons (1997-2009), found that influenza deaths were highest in older and high-risk individuals. In terms of deaths from influenza and pneumonia, CDC statistics[7] show that between 1999 and 2011 there were on average some 20 deaths each year (high of 23 and low of 17) per 100,000 of the US population. Other recent data and CDC statements indicate there is no reason to think that there has been any major change between 2011 and 2014. Over the 1999-2011 period the death rate per 100,000 was 35 for the group aged 65-74; 140 for the group aged 75-84; and 600 for the 85+ group. There was also a higher than average death rate for infants of less than 1 year. Adults between 20 and 50 obviously had much lower rates. The figures do not distinguish between those who had received a vaccine shot in a particular year and those who had not; nor any who had a history of previous flu shots. The greatest burden of influenza disease occurs in persons aged 65 years and older despite achieving an immunization rate of 65 to 70 percent in this population.

It is important to note that the impact of seasonal flu can be as serious as impact of pandemic flu. Seasonal influenza has significant health and economic impacts, with a cumulative impact as serious as a pandemic. According to the World Health Organization (WHO), annual seasonal influenza epidemics result in about 3 million to 5 million cases of severe illness and about 250,000 to 500,000 deaths worldwide, which is likely an underestimation. As noted in a 2012 report by the Center for Infectious Disease Research & Policy, "[T]hese figures indicate that the cumulative health impact of seasonal influenza over the last century rivals the potentially explosive, but time-limited, impact of the four pandemics of the past 100 years."[8]

B. Influenza Strains and Detection

The influenza virus is a single-stranded RNA virus.[9] However, there are three types of influenza virus (A, B, and C) that are distinguished by their different main nucleoproteins.[10] Although all three types of influenza virus have the capacity to infect humans, types A and B are the deadliest. In particular, influenza A H3N2 virus poses the greatest concern. When the H3N2 flu viruses are predominant, it tends to cause more severe illness and hospitalization among the

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[7] www.cdc.gov/nchs/faststats/deaths.htm

[8] Center for Infectious Disease Research & Policy, University of Minnesota, The Compelling Need for Game-Changing Influenza Vaccines: An Analysis of the Influenza Vaccine Enterprise and Recommendations for the Future, 11 (October 2012).

[9] B. Tesfayesus, et al., "Influenza: How serious is it?" Clinical Advisor (November 9, 2015) http://www.clinicaladvisor.com/influenza-how-serious-is-it/printarticle/452733/

[10] http://www.cdc.gov/flu/about/viruses/types.htm. In addition, each of these viruses are further identified by two proteins: hemagglutinin (H) and neuraminidase (N). These proteins play a key role in causing the flu virus by neutralizing antibodies.

elderly. According to one study, the H3N2 A strain accounted for a seasonal average of 71 percent influenza-attributable deaths compared to the other strains.[11]

Recently, the influenza strains have grown increasingly complex and have been distributed more broadly across the globe. In February 2015, the WHO noted, "The diversity and geographical distribution of influenza viruses currently circulating in wild and domestic birds are unprecedented since the advent of modern tools for virus detection and characterization. The world needs to be concerned."[12] In 2015, so many new types of flu, including highly infectious strains, have emerged that public health officials around the world are racing to keep up with the viruses and spot the dangers they may pose.[13] For example, new influenza A viruses are constantly emerging from animal reservoirs, and there has been a tenfold increase in the number of human infections with different novel influenza A viruses since the 1990s.[14]

The news of this array of genetic forms of influenzas is partly a result of improved surveillance measures.[15] However, many scientists believe that the pace of evolution in influenza is speeding up because of human movement and trade along the Asian flyway, giving more opportunities for various types of flu to comingle, jumble their RNA genetic material, and form novel strains.[16] This in turn is making it harder for scientists to predict which forms of influenza are likely to hit human populations, accurately predict what type of vaccine is likely to be effective for that season, and anticipate the movement of flu viruses from wild birds to domestic fowl, fowl to humans, humans to swine, and swine back to humans. The consequences from the emergence of so many novel viruses "for animal and human health are unpredictable yet potentially ominous."[17]

The speed in which influenza can be detected is a key concern. While the complexity and number of flu viruses is increasing, antiquated testing may delay detection of mutations in certain seasonal influenza viruses. Antigenic testing for strain selection is still based on the HAI assay, which was developed in the 1940s. In 2011, a WHO Conference report acknowledged this assay had performance issues in recognizing emerging changes in the H3N2 viruses.[18] Poor performance of these H3N2 strains in the HAI assay may delay recognition that a new antigenic variant of H3N2 is emerging.

C. The Seasonal Flu Vaccine: Development and Effectiveness

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[11] Matias, *supra*, note 4.
[12] WHO, "Warning signals from the volatile world of influenza viruses," February 2015. http://www.who.int/influenza/publications/warningsignals201502/en/
[13] L. Garrett, The Year of the Flu, February 4, 2015. http://www.cfr.org/public-health-threats-and-pandemics/year-flu/p36079
[14] Institute of Medicine, Rapid Medical Countermeasure Response to Infectious Diseases, Workshop Summary (2015)(referencing presentation by Dr. Jacqueline Katz, deputy director (acting) of the Influenza Division at the CDC.
[15] Id.
[16] L. Garrett, note 9.
[17] WHO, note 8.
[18] WHO Conference Report, Strengthening the influenza vaccine virus selection and development process, Outcome of the 2nd WHO Informal Consultation for Improving Influenza Vaccine Virus Selection held at the Centre International de Conferences (CICG) Geneva, Switzerland, 7 to 9 December 2011, 31 Vaccine 3209, 3213 (2013).

The primary method for preventing influenza is annual vaccination. CDC recommends annual vaccinations for everyone aged 6 months or older. According to a CDC study published in the journal *Vaccine*, the seasonal flu vaccine prevented more than 40,000 flu-associated deaths in the United States during a nine-year period, from 2005-2006 through 2013-2014.[19]

For the 2011-2012 season, about 42 percent of Americans aged 6 months and over were vaccinated.[20] Data from the 2012-2013 season showed that 45 percent of Americans 6 months or older got vaccinated.[21] For 2013-2014 season, the overall vaccination rate was 46 percent.[22] The estimate for this season as of November 2014 was 46.2 percent. According to the CDC FY 2015 Congressional Justification, the CDC set a performance measure for the long term objective to increase the proportion of adults (18 and older) who are vaccinated annually against influenza. In FY 2013, the CDC set the target at 42 percent but that target was not met. The FY 2014 target was 50 percent and the goal for FY 2015 was 53 percent.

HHS has set a goal for states to vaccinate 70 percent of their population as part of the Healthy People 2020 initiative. According to experts, vaccination rates need to be generally above 70 percent for "herd immunity" effects – which limit the spread and protect those without immunity – to become apparent. If all seniors received a newly available high-dose version of the flu shot, flu cases among this high-risk population could drop 25 percent.[23]

Because circulating influenza virus strains change, a new vaccine is produced and administered each year to protect against strains expected to be most prevalent that year. "Influenza is a very challenging virus in that its surface proteins change constantly to evade both our immune systems and vaccines. As a result of these changes, in most years, at least one of the strains in the vaccine must be changed to keep up with changes in the circulating virus."[24] Each year, public health experts, including those from FDA, the WHO, and CDC, study influenza virus samples and global disease patterns to identify virus strains likely to cause the most illness during the upcoming season. Based on that information and the recommendations of FDA's Vaccines and Related Biological Products Advisory Committee (VRBAC), FDA selects the strains for inclusion in the annual influenza virus – two strains of influenza type A and one strain of influenza type B – to include in the annual influenza vaccine.[25] Because of the lead time

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[19] I. Foppa, et al., "Deaths averted by influenza vaccination in the U.S. during the seasons 2005/06 through 2013/14, 33 Vaccine 3003 (March 23, 2015), www.sciencedirect.com/science/article/pii/S0264410X15002315.

[20] Written testimony of Dr. Thomas Frieden, CDC Director, before the House Energy and Commerce Subcommittee on Oversight and Investigations, February 13, 2013 at 8 (indicating that the rate was 52 percent but that was for the subgroup of Americans aged 6 months to 17).

[21] Flu Vaccination Coverage, United States, 2012-13 Influenza Season, http://www.cdc.gov/flu/fluvaxview/coverage-1213estimates.htm.

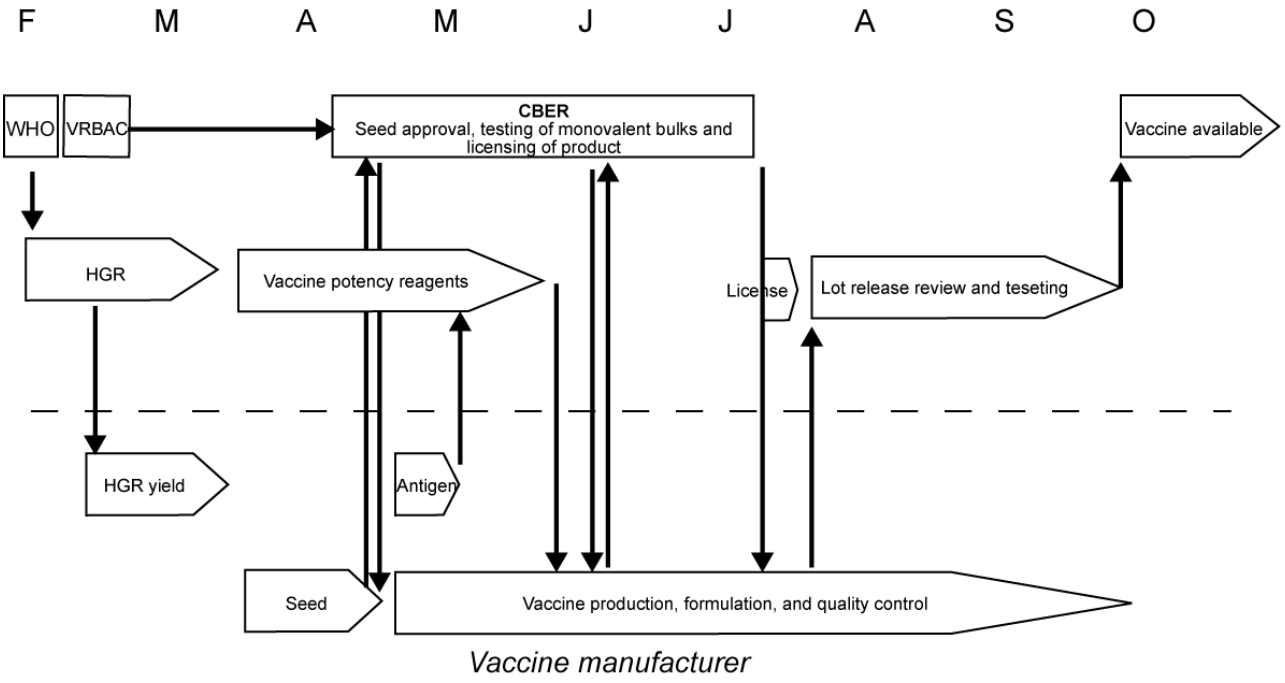
[22] 2010-11 through 2013-14 State, Regional, and National Vaccination Trend Report, http://www.cdc.gov/flu/fluvaxview/reports/reporti1314/trends/index.htm.

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

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

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

needed for manufacturing flu vaccine, the decisions on strain selection need to be made usually by the end of February for vaccine to be available later in the year for the flu season in the U.S.



Above is a graphic illustration[26] of the annual timeline for the U.S. vaccine production process.

For last year's flu season, there were about 150 million doses of flu vaccine available annually in the U.S., with about 140 million doses from egg-based manufacturing and 10 million doses from cell- and recombinant-based. The estimated lead times to first dose for each type of manufacturing are as follows: egg-based, 22-24 weeks; cell-based, 16-17 weeks; and recombinant, 12-15 weeks. For this year's flu season, HHS subject matter experts advised committee staff last week that there would be a record supply of 170 million doses of flu vaccine. Although there was no specific estimate of the number of egg-based doses, experts expected that more than 90 percent of the vaccine supply would be egg-based.

Seasonal flu vaccination typically has an effectiveness[27] rate in the range of 50-60 percent.[28] Seasonal flu vaccine effectiveness studies show a low effectiveness rate of 10 percent

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

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

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

(in high-risk populations) for the 2004-2005 season with a high rate of 60 percent (general population) in the 2010-2011 season. Vaccination, even with effectiveness of about 60 percent, has been shown to reduce flu-related illness, antibiotic use, time lost from work, hospitalizations, and deaths. However, vaccine efficacy was less than 40 percent during 4 out of the past 10 years.[29] A meta-analysis of 60 past studies of flu vaccine effectiveness presented at an infectious disease conference in San Diego last month found only 38 percent effectiveness against the H3N2 influenza virus.[30]

Lower effectiveness may be attributable, in part, to antigenic drift. "Antigenic drift" refers to small changes in the genes of influenza viruses that happen continually over time as the virus replicates.[31] These small genetic changes usually produce viruses that are closely related to one another.[32] While these small genetic changes can accumulate over time, this can lead to viruses that look different to a person's immune system. The antibodies created against older viruses no longer recognize the "newer" virus, and the person can get sick again.[33]

Egg adaptation may also contribute to lower effectiveness of the vaccine. Vaccine effectiveness is generally interpreted in the context of vaccine match/mismatch to circulating strains that have mutated to explain reduced protection. However, in 2014, a study funded by the Canadian Institutes of Health Research, found that during the 2012-2013 flu season the low vaccine effectiveness was related to mutations in the egg-adapted H3N2 vaccine strain rather than antigenic drift in circulating viruses.[34] Although there is no significant antigenic drift in the 2015-2016 strain selection, there are still concerns about the H3N2 strain in this season's vaccine. Publicly available data from the WHO Collaborating Center in the United Kingdom generated in February 2015, prior to the Northern Hemisphere selection, showed that although the mammalian cell-adapted A/Switzerland/9715293/2013 would provide reasonable coverage of recent H3N2 strains, it undergoes a significant antigenic change upon egg adaptation that greatly reduce the coverage. Because eggs are used to propagate the viruses that the WHO sends to U.S. vaccine manufacturers and because most of the influenza vaccine supply is produced in eggs, the mismatch due to egg-adaptation could have an important impact on vaccine match this season, even if there is little antigenic drift.

D. The 2014-2015 Seasonal Influenza Vaccine Mismatch

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[29] Fluview, CDC, Table of Adjusted vaccine effectiveness estimates for influenza seasons from 2005-2015.
[30] S. Zhang, "Scientists Found a Flu Vaccine – Now They Have to Fix It," Wired (October 9, 2015). http://www.wired.com/2015/10/scientists-pinpoint-flu-vaccine-flaw-h3n2/. See also H. Branswell, "Weak link discovered in flu vaccine," STAT, (October 7, 2015) https://www.bostonglobe.com/lifestyle/health-wellness/2015/10/06/researchers-find-weak-link-flu-vaccine/sJrqYQ2eFdbeFEMFXLEViO/story.html.
[31] Response attached to letter from Thomas R. Frieden, MD, MPH, Director of the CDC to The Honorable Fred Upton, Chairman, House Energy and Commerce Committee, et al., April 9, 2015. In contrast, "antigenic shift" is an abrupt, major change in the influenza A viruses that emerge from an animal population. Because the majority of people would have no immunity to the new virus, a much higher population attack rate – the pandemic scenario - would be expected.
[32] Id.
[33] Id.
[34] D. Skowronski, et al., Low 2012-13 Influenza vaccine Effectiveness Associated with Mutation in the Egg-Adapted H3N2 Vaccine Strain Not Antigenic Drift in Circulating Viruses, PLOS (March 25, 2014). http://journals.plos.org/plos.org/plosone/article?id=10.1371/journal.pone0092153

The U.S. experienced a severe flu season in 2014-2015 because that year's vaccine did not protect well against the dominant H3 A strain of influenza, which mutated after the vaccine-production process began for the 2014-2015. Given the lead time needed for manufacturing and regulatory compliance, there was not enough time to modify the vaccine and restart the manufacturing.

An analysis of the 2014-2015 seasonal flu vaccine showed only 19 percent effectiveness for the overall U.S. population — much less so for most American adults, with close-to-final statistics demonstrating only 12 percent effectiveness for those 18-49 years old and 14 percent for those 50 years or older. This is the lowest rate since CDC has collected standardized, more accurate data of effectiveness rates in the last four to five years.

The lower effectiveness is due to significant mutations in a key flu strain (the dominant H3N2 A strain) that occurred sometime after the strain selection decision for the U.S. vaccine was made in February and before the onset of this year's flu season in the U.S. This occasionally occurs. For example, CDC stated during a staff briefing that the 1999 seasonal flu vaccine had near zero effectiveness because of drift in the strain from mutations.

CDC first detected the drift of the H3N2 A strain in March 2014, but the drift was at an insignificant level, and not yet considered evidence of a distinctive and meaningful drift. Sometime in May, CDC found that the drift resulted in a 17 percent mismatch, a level of concern but not unambiguous evidence of a significant drift.[35] CDC indicated to staff that a drift in the range of 20 to 30 percent would be considered significant. CDC later confirmed a drift of 36 percent for the summer, but CDC did not find a qualified candidate virus until September. By September 2014, the mismatch was about 50 percent, and a vaccine candidate for the new strain was identified. As a result, the WHO recommended replacing the H3 A strain in the seasonal flu vaccine for the Southern hemisphere. The drift wound up at about a 66 percent mismatch level.

For the 2015-2016 seasonal flu vaccine for the U.S., CDC reported to the Committee that through late May, more than 90 percent of the U.S. influenza viruses tested by CDC were antigenically like or similar to the vaccine viruses.

E. Committee's Continuing Oversight

Following the Subcommittee's hearing on February 3, 2015, bipartisan committee leaders sent letters on March 9, 2015, to the CDC, FDA, NIH, BARDA, and the Secretary of Department

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

of Health and Human Services (HHS). They asked each agency additional questions about the U.S. public health response to last year's flu season, as well as what ways the agencies could improve preparedness for seasonal influenza. On July 31, 2015, bipartisan committee leaders sent another letter to HHS Secretary Sylvia Burwell with additional questions and a request for documents on recommendations or lessons learned from last year's flu season. HHS provided answers to the questions in a September 30, 2015 response. Later, HHS produced a May 6, 2015 memorandum sent to Secretary Burwell on influenza process improvements.

F. Improvements in U.S. Response to Seasonal Influenza

Since the Subcommittee's hearing in February about the 2014-2015 vaccine mismatch, there are indications of seasonal influenza being made a greater priority and getting more attention than in the past. First, the HHS Influenza Risk Management Group, which has primarily met over the last 12 years on pandemic influenza issues, has been including seasonal influenza issues on the agenda during meetings in 2015. Second, HHS Secretary Sylvia Burwell, through her counselors, requested that HHS experts recommend actions to mitigate the seasonal influenza mismatch problem. Third, on May 6, 2015, a memorandum of influenza process improvements was sent to Secretary Burwell. Finally, earlier this month, HHS held a table top exercise with HHS agencies and vaccine manufacturers, to solicit their individual opinions. The exercise outcome is expected to inform an HHS action plan for rapid development and manufacturing of a revised seasonal influenza vaccine as a strain change or a separate monovalent vaccine.

Here are some of the key actions being taken to improve seasonal flu preparedness:

- *Technological improvements*. Vaccine manufacturers are in the process of adopting several process improvements for pandemic vaccine. HHS anticipates and will ask that these improvements also be applied to seasonal influenza vaccine manufacturing. Application of these improvements to seasonal influenza could save four to six weeks in the manufacturing and formulation process. If successful, strain selection decisions could be made with surveillance information closer to the beginning of the influenza season.

- *Use of the Influenza Risk Assessment Tool (IRAT).* HHS uses the IRAT for decisions to make limited amounts of vaccine in response to emerging, potentially-pandemic strains. The HHS Influenza Risk Management Group, using the IRAT as a model, is working to develop a risk assessment method within the next 15 months to guide recommendations about whether to change seasonal vaccine strain composition between the WHO recommendation and June.

- *Monovalent rescue vaccine.* Recent discussions at the Flu Risk Management Meeting (FRMM), which is coordinated by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR), have included considerations to determine under that circumstances a monovalent rescue vaccine would be pursued due to a drifted seasonal influenza strain. Factors that could impact that decision include

manufacturing capabilities and disease severity. In 1986, FDA approved a monovalent influenza vaccine to supplement the trivalent influenza vaccine to address a drift of the H1N1 strain.[36] Approximately 7 million doses of the 1986 monovalent vaccine were manufactured or distributed late in 1986.[37]

- *Late season change to tri- or quadrivalent vaccine.* HHS has taken a series of steps to increase the probability that a late season change to tri- or quadrivalent vaccine could be made. These changes would also enable faster production of a monovalent vaccine should it be needed. Some of these key steps include: FDA making more potency assay reagents to facilitate the production of new vaccines, CDC (with WHO) helping improve availability of additional vaccine viruses, CDC (with WHO) enhancing global surveillance of circulating human and avian influenza viruses.

- *Increased communication.* More frequent and comprehensive communication with HHS leadership and FDA has been implemented, and FDA has done likewise with the Chair of its Vaccines and Related Biological Products Advisory.

- *Antivirals and other strategies*. As during the 2014-2015 influenza season, CDC emphasizes the use of antiviral medications as a "second line of defense," promotes pneumococcal vaccination for seniors to help mitigate the complications of flu in the elderly, and stresses the importance of everyday preventive actions like covering coughs, social distancing, and frequent hand washing.

G. Pandemic Influenza

As noted in Dr. Robin Robinson's February 3, 2015, testimony before the Subcommittee, preparedness and response plans for seasonal and pandemic influenza "are inextricably interwoven; what we do in one area directly affects what we do in the other." Thus, pandemic flu preparedness should be noted in the context of the hearing.

An influenza pandemic can occur when a novel, non-human influenza virus becomes able to spread efficiently through human-to-human transmission. The viruses circulate in birds or other animals, so there is little to no immunity against these viruses among people. Examples include the avian "bird flu" influenzas H5N1 and H7N9. The Centers for Disease Control and Prevention refers to influenza viruses that have the potential to cause a pandemic as "influenza viruses with pandemic potential."[38]

U.S. public health agencies rely on many of the same tools to identify and track seasonal influenza viruses and influenza viruses with pandemic potential. These preparedness efforts include "ongoing surveillance of human and animal influenza viruses, risk assessments of

[36] Letter from Thomas A. Kraus, FDA Associate Commissioner for Legislation to The Honorable Fred Upton, Chairman, House Energy and Commerce Committee, et al., April 8, 2015.
[37] CDC , 37 CDC Morbidity and Mortality Weekly Report 469 (August 12, 1988).
[38] CDC Resources for Pandemic Flu, Centers for Disease Control and Prevention, http://www.cdc.gov/flu/pandemic-resources/ (last visited Nov. 13, 2015).

influenza viruses with pandemic potential, and the development and improvement of preparedness tools" for public health practitioners.[39]

The HHS Influenza Risk Management Group, comprised of officials from BARDA, HHS Office of the Assistant Secretary for Health (OASH), NIH, CDC, and FDA, also meets monthly to discuss updates on seasonal and pandemic influenza issues, including preparedness issues.

HHS maintains three influenza preparedness documents—the 2005 *Pandemic Influenza Plan*, the 2009 *H1N1 Influenza Improvement Plan*, and the Pandemic Annex to the HHS All-Hazards Plan. The 2005 *Pandemic Influenza Plan* acts "as a blueprint for all HHS pandemic influenza preparedness planning and response activities."[40] The 2009 *H1N1 Influenza Plan*, released in 2012, communicated "HHS' priorities for modifying and updating the prior 2005 *HHS Pandemic Influenza Plan*, informed by lessons learned from the 2009 H1N1" influenza pandemic.[41] The Pandemic Annex to the HHS All-Hazards Plan is one of multiple threat-specific annexes that augment the overall plan.[42] While HHS is currently updating all three plans, the Department does not expect the revised plans to be complete until 2016.

III. ISSUES

The following issues will be examined at the hearing:

- What were the lessons learned from the last season's flu vaccine mismatch?
- How effective are the steps that HHS is taking to improve seasonal influenza preparedness in addressing the lessons learned?
- How can better and more effective flu vaccines be made?
- What communications or guidance would be effective in helping increase the use of antiviral medications and reduce the use of antibiotics in the treatment for influenza?
- What research needs to be done to determine whether a low level of effectiveness of a seasonal flu vaccine could be substantially increased if the vaccine was adjuvanted?[43]

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[39] CDC Resources for Pandemic Flu, Centers for Disease Control and Prevention, http://www.cdc.gov/flu/pandemic-resources/ (last visited Nov. 13, 2015).
[40] U.S. Dep't of Health & Human Serv., *HHS Pandemic Influenza Plan* 2 (Nov. 2005), *available at* http://www.flu.gov/planning-preparedness/federal/hhspandemicinfluenzaplan.pdf.
[41] U.S. Dep't of Health & Human Serv., 2009 H1N1 Influenza Improvement Plan 3 (May 29, 2012), *available at* http://www.phe.gov/Preparedness/mcm/h1n1-retrospective/Documents/2009-h1n1-improvementplan.pdf.
[42] Letter from Dr. Nicole Lurie, Assistant Sec'y for Preparedness & Response, U.S. Dep't of Health & Human Serv., to Hon. Fred Upton, Chairman, H. Comm. on Energy & Commerce (July 31, 2015).
[43] No adjuvanted seasonal influenza vaccine has ever been licensed in the U.S. to date. Dr. Andrew Pavia stated that with an adjuvanted vaccine "we probably could have made the mistake we made [in the 2014-15 flu] year and instead of efficacy declining from 65 percent to 23 percent, it might have only declined to 40-50 percent." Brookes, et al., supra note 16.

IV. STAFF CONTACTS

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