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

March 6, 2018

TO: Members, Subcommittee on Oversight and Investigations

FROM: Committee Majority Staff

RE: Hearing entitled "Examining the U.S. Public Health Preparedness for and Response Efforts to Seasonal Influenza."

I. Introduction

The Subcommittee on Oversight and Investigations will hold a hearing on Thursday, March 8, 2018, at 10:00 a.m. in 2123 Rayburn House Office Building. The hearing is entitled "Examining U.S. Public Health Preparedness for and Response Efforts to Seasonal Influenza." The Subcommittee will examine the U.S. Department of Health and Human Services' efforts to combat seasonal influenza, develop an effective influenza vaccine, and to prepare a long-term strategy to improve seasonal influenza preparedness.

II. Witnesses

- Anne Schuchat, M.D. (RADM, USPHS), Acting Director, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services;
- Anthony S. Fauci, M.D., Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Department of Health and Human Services;
- Rick A. Bright, Ph.D., Deputy Assistant Secretary for Preparedness and Response, Director of the Biomedical Advances Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response, U.S. Department of Health and Human Services; and
- Scott Gottlieb, M.D., Commissioner of Food and Drugs, U.S. Food and Drug Administration, U.S. Department of Health and Human Services.

III. Background

A. Overview of Seasonal Influenza in the United States

Influenza (the "flu") is a contagious respiratory illness caused by different virus strains and can range in severity from mild to deadly. In both its seasonal and pandemic forms, influenza is an ongoing public health concern and is a leading cause of death in the United

States.[1] The number of illnesses, hospitalizations, and deaths per year can vary depending on several factors, including but not limited to, the severity of the flu season, characteristics of the prevalent viruses, and the effectiveness of the vaccine. The Centers for Disease Control and Prevention (CDC) estimates that, on an annual basis since 2010, influenza has resulted in between 9.2 million and 60.8 million illnesses, 140,000 and 710,000 hospitalizations, and 12,000 and 56,000 deaths.[2] As noted in CDC's 2018 Congressional Budget Justification, a 2007 study estimated that more than $10 billion is spent each year in direct medical costs for hospitalizations and outpatient visits from seasonal influenza-related complications.[3]

Although CDC estimates the number of flu-associated deaths, CDC does not calculate the exact number of individuals that die each year from the seasonal flu.[4] The agency cannot calculate this number for a variety of reasons, including but not limited to the fact that: (1) states are not required to report individual seasonal flu cases or deaths of people aged 18 years and older to CDC; (2) many influenza-related deaths, such as from pneumonia, may not include any mention of influenza on the death certificate; (3) it can be difficult to identify which cases to include in an analysis since many patients (especially the elderly) may die from pneumonia unrelated to influenza; and (4) 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 in calculating the precise number of flu-related deaths, researchers use a variety of modeling techniques to estimate deaths. CDC looks at two categories of underlying cause of death information listed on death certificates to estimate the number of flu-associated deaths: (1) pneumonia and influenza (P&I) causes; and (2) respiratory and circulatory (R&C) causes.[5]

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[1] Seasonal flu is an outbreak that follows predictable seasonal patterns. Pandemic flu is a worldwide outbreak of a new form of flu virus, which can spread easily from person to person because most people have little to no immunity. Centers for Disease Control and Prevention, *How is Pandemic Flu Different from Seasonal Flu?* (last updated Dec. 9, 2016), https://www.cdc.gov/flu/pandemic-resources/basics/about.html.

[2] Based on 2015 data, CDC estimated that the number of deaths in 2015 caused by influenza and pneumonia was 57,062. U.S. Dep't of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *Health, United States, 2016, With Chartbook on Long-term Trends in Health* (2016), https://www.cdc.gov/nchs/data/hus/hus16.pdf#019; Centers for Disease Control and Prevention, *Estimated Influenza Illnesses, Medical Visits, Hospitalizations, and Deaths Averted by Vaccination in the United States* (last updated Apr. 19, 2017), https://www.cdc.gov/flu/about/disease/2015-16.htm; Centers for Disease Control and Prevention, *Estimating Seasonal Influenza-Associated Deaths in the United States—Questions and Answers* (last updated Jan. 29, 2018), https://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm; Centers for Disease Control and Prevention, *Deaths and Mortality* (last updated May 3, 2017), https://www.cdc.gov/nchs/fastats/deaths.htm; Centers for Disease Control and Prevention, *Seasonal Influenza-Associated Hospitalizations in the United States* (last updated at Dec. 9, 2016), https://www.cdc.gov/flu/about/qa/hospital.htm.

[3] Centers for Disease Control and Prevention, *FY 2018 Congressional Justification*, at 46 (2018), https://www.cdc.gov/budget/documents/fy2018/fy-2018-cdc-congressional-justification.pdf; *See also* Molinari, et al., *The annual impact of seasonal influenza in the US: measuring disease burden and costs*, VACCINE Volume 25 Issue 27 (Jun. 28, 2007).

[4] Centers for Disease Control and Prevention, *Estimating Seasonal Influenza-Associated Deaths in the United States—Questions and Answers* (last updated Jan. 29, 2018), https://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm.

[5] *Id*.

While the flu may result in death or hospitalization, most individuals that get the flu only have a mild illness and will recover in less than two weeks.[6] Examples of flu-related complications include bronchitis, pneumonia, ear infections, sinus infections, and worsening of chronic health conditions. Those individuals that are at high risk for developing flu-related complications include, but are not limited to, children younger than 5 years of age, adults 65 years of age and older, pregnant women, residents of long-term care facilities, American Indians and Alaska Natives, and individuals with certain medical conditions.[7] Although individuals aged 65 and older are more likely to receive the flu vaccine than younger adults, hospitalization rates for the flu are likely to be highest among the elderly. For example, for the 2014-2015 flu season, 38 percent of people aged 18-64 years old received the vaccination while 66.7 percent of people aged 65 years and older received the vaccination.[8] About 75 percent of the estimated hospitalizations for the 2014-2015 flu season, however, occurred in individuals aged 65 years and older.[9]

Overall, 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 and 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."[10]

B. Types of Influenza and Influenza Detection

The influenza virus is made up of single-stranded ribonucleic acid (RNA) segments that are coated by a nucleoprotein.[11] The four types of influenza viruses (A, B, C, and D) are primarily distinguished by their different main nucleoproteins.[12] Influenza types A, B, and C have the capacity to infect humans whereas influenza type D primarily infects cattle and is not

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[6] Centers for Disease Control and Prevention, *People at High Risk of Developing Flu-Related Complications* (last updated Jan. 23, 2018), https://www.cdc.gov/flu/about/disease/high_risk.htm.
[7] *Id*.
[8] Centers for Disease Control and Prevention, *Flu Vaccination Coverage, United States, 2014-15 Influenza Season* (last updated Jun. 23, 2016), https://www.cdc.gov/flu/fluvaxview/coverage-1415estimates.htm#age-group-adults.
[9] Centers for Disease Control and Prevention, *Estimated Influenza Illnesses and Hospitalizations Averted by Vaccination – United States, 2014-15 Influenza Season* (last updated Feb. 17, 2017), https://www.cdc.gov/flu/about/disease/2014-15.htm.
[10] Center for Infectious Disease Research and Policy, University of Minnesota, *The Compelling Need for Game-Changing Influenza Vaccines: An Analysis of the Influenza Vaccine Enterprise and Recommendations for the Future*, at 11 (October 2012).
[11] University of Pittsburgh Schools of the Health Sciences, *50-year-old flu virus model revamped, revealing pandemic prediction possibilities*, SCIENCE DAILY (Jul. 13, 2017), https://www.sciencedaily.com/releases/2017/07/170713154853.htm; Nara Lee, et al., *Genome-wide analysis of influenza viral RNA and nucleoprotein association*, NUCLEIC ACIDS RESEARCH Volume 45, Issue 15 (Sept. 6, 2017).
[12] Centers for Disease Control and Prevention, *Types of Influenza Viruses* (last updated Sept. 27, 2017), https://www.cdc.gov/flu/about/viruses/types.htm.

known to infect or cause illness in humans.[13] Influenza types A and B are the two main types of viruses that cause seasonal epidemics and typically pose the most serious public health threat. Influenza type C infections are not believed to cause epidemics and instead typically cause mild respiratory illness.[14]

The CDC adheres to an internationally accepted naming convention for influenza viruses that was accepted by the World Health Organization (WHO) in 1979.[15] Each influenza virus is named according to: (1) the antigenic type (*e.g.*, A, B, C); (2) the host of origin for viruses that did not originate in humans (*e.g.*, swine, chicken, etc. (no host of origin designation is provided for human-origin viruses)); (3) geographical origin (*e.g.*, Denver, Taiwan, etc.); (4) strain number (*e.g.*, 15, 7, etc.); (5) year of isolation (*e.g.*, 2009, etc.); and (6) the hemagglutinin (H) and neuraminidase (N) antigen in parentheses for influenza type A viruses (*e.g.*, (H1N1) (influenza types B and C do not receive these subtype classifications)).[16]

Recently, influenza strains have grown increasingly complex and have been distributed more broadly across the globe. In February 2015, the WHO noted that the world needed to be concerned about the diversity and geographical distribution of influenza viruses:

> The current global influenza situation is characterized by a number of trends that must be closely monitored. These include: an increase in the variety of animal influenza viruses co-circulating and exchanging genetic material, giving rise to novel strains… 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.[17]

The news of this array of genetic forms of influenza is partly a result of improved surveillance measures.[18] Many scientists, however, 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, mix their RNA genetic material, and form novel strains.[19] This in turn is making it harder for scientists to predict which forms of influenza are likely to hit human populations during certain seasons, 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.

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[13] *Id.*
[14] *Id.*
[15] *Id.*
[16] *Id.*
[17] World Health Organization, *Warning signals from the volatile world of influenza viruses* (Feb. 2015), http://www.who.int/influenza/publications/warningsignals201502/en/.
[18] Lauren S. Polansky, et al., Centers for Disease Control and Prevention, *Improved Global Capacity for Influenza Surveillance*, EMERGING INFECTIOUS DISEASES Volume 22, Number 6 (June 2016).
[19] Laurie Garrett, *The Year of the Flu*, COUNCIL ON FOREIGN RELATIONS (Feb. 4, 2015), https://www.cfr.org/expert-brief/year-flu.

The consequences from the emergence of so many novel viruses "for animal and human health are unpredictable yet potentially ominous."[20]

Moreover, the influenza viruses constantly change through antigenic drift and antigenic shift.[21] Antigenic drift refers to small changes in the genes of influenza viruses that happen continually over time as the virus replicates.[22] Antigenic shift occurs when there is an abrupt, significant change in the influenza A virus resulting in a new H and/or new H and N proteins. Because the H and N antigens can undergo antigenic shifts or drifts and mutate frequently, influenza type A typically causes the most severe outbreaks. Indeed, new influenza type 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.[23] One specific subtype of influenza type A, H3N2, has a faster mutation rate than H1N1 or influenza B viruses, and this fast mutation rate can make it even more difficult to make an effective vaccine during some flu seasons.[24] For example, during the 2014-2015 flu season, the prevalent strain of H3N2 was different than the strain used during the season's vaccine development.[25]

Because of the potential for changes in the circulating influenza viruses, close monitoring of influenza viruses is required to evaluate the potential impact of the seasonal flu on public health. CDC uses different tests to characterize influenza viruses, including genomic sequencing and Hemagglutinin Inhibition Assay (HAI/HI assay).[26] For samples collected and submitted to U.S. laboratories from October 1, 2017 to February 17, 2018, CDC has antigenically or genetically characterized 1,599 influenza viruses, including 350 influenza A(H1N1)pdm09 viruses, 779 influenza A(H3N2) viruses, and 470 influenza B viruses.[27] For H3N2, the analysis for the 2017-2018 flu season "revealed extensive generic diversity with multiple clades/subclades co-circulating."[28]

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[20] World Health Organization, *supra* note 17.
[21] Centers for Disease Control and Prevention, *How the Flu Virus Can Change: "Drift" and "Shift,"* (last updated Sept. 27, 2017), https://www.cdc.gov/flu/about/viruses/change.htm.
[22] *Id*.
[23] National Academies of Sciences, Engineering, Medicine, *Rapid Medical Countermeasure Response to Infectious Diseases, Workshop Summary*, at 48 (Oct. 12, 2015), https://www.nap.edu/read/21809/chapter/6?term=1990#48.
[24] Helen Branswell, *'The problem child of seasonal flu': Beware this winter's virus*, STAT NEWS (Jan. 8, 2018), https://www.statnews.com/2018/01/08/flu-virus-h3n2/.
[25] Laurie Garrett, *The Year of the Flu*, COUNCIL ON FOREIGN RELATIONS (Feb. 4, 2015), https://www.cfr.org/expert-brief/year-flu; Hearing before the U.S. House of Representatives, Committee on Energy and Commerce, "U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?" (Nov. 19, 2015).
[26] *Id*.
[27] *Id*. Some researchers have found that the H3N2 virus poses significant health risks and results in more fatalities and hospitalizations than other influenza viruses. Dan Gray, *2018 Flu Season Off to a Strong, Potentially Dangerous Start*, HEALTHLINE (Jan. 3, 2018), https://www.healthline.com/health-news/2018-flu-season-potentially-dangerous-start#1.
[28] Laurie Garrett, *supra* note 25.

C. Seasonal Flu Vaccine: Development and Effectiveness

i. Seasonal Influenza Vaccine Development

The flu vaccine must be reformulated on an annual basis to protect against strains expected to be most prevalent that year since circulating influenza virus strains constantly change.[29] Each year, public health experts, including those from the Food and Drug Administration (FDA), 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.[30] In collaboration with other partners, WHO recommends the specific vaccine viruses that should be included in the next season's influenza vaccines in the northern hemisphere every February (WHO made recommendations for the 2018-2019 flu season on February 22, 2018).[31] The FDA then selects the strains for inclusion in the annual influenza virus that is sold and distributed in the United States based on that information and the recommendations of FDA's Vaccines and Related Biological Products Advisory Committee (VRBAC).[32]

Most flu vaccines are injectable and include inactivated influenza vaccines and recombinant influenza vaccines.[33] Typically, the influenza vaccine protects against three or four different flu viruses.[34] There are three different production technologies approved by the FDA for injectable influenza vaccines: (1) egg-based flu vaccine; (2) cell-based flu vaccine; and (3) recombinant flu vaccine.[35] The egg-based manufacturing process, which has been used for more than seventy years and takes about 22 to 24 weeks to produce, is the most common way that flu vaccines are manufactured in the U.S. The cell-based production process, approved by FDA in 2012, takes about 16 to 17 weeks to manufacture the vaccine. The recombinant flu vaccine manufacturing process, approved by FDA in 2013, can produce flu vaccines in the shortest amount of time at about 12 to 15 weeks.

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[29] Centers for Disease Control and Prevention, *Selecting Viruses for the Seasonal Influenza Vaccine* (last updated May 4, 2016), https://www.cdc.gov/flu/about/season/vaccine-selection.htm.

[30] In the northern hemisphere, seasonal influenza may begin as early as August and generally diminishes by April. Typically, influenza activity peaks between December and February in the United States but may peak later in the season. Centers for Disease Control and Prevention, *Estimated Influenza Illnesses, Medical Visits, Hospitalizations, and Deaths Averted by Vaccination in the United States* (last updated Apr. 19, 2017), https://www.cdc.gov/flu/about/disease/2015-16.htm.

[31] Centers for Disease Control and Prevention, *Selecting Viruses for the Seasonal Influenza Vaccine*, *supra* note 29.

[32] Robert Lowes, *First Quadrivalent Flu Vaccine Approved, Debuts Fall 2013*, MEDSCAPE (Mar. 1, 2012), https://www.medscape.com/viewarticle/759517.

[33] Immunization Action Coalition, *Influenza Vaccine Products for the 2017-2018 Influenza Season* (last visited Mar. 2, 2018) http://www.immunize.org/catg.d/p4072.pdf.

[34] The trivalent influenza vaccine protects against three different influenza viruses (including an influenza A(H1N1) virus, an influenza A(H3N2) virus and one influenza B virus) and the quadrivalent influenza vaccine protects against four influenza viruses (including an influenza A(H1N1) virus, an influenza A(H3N2) virus and two influenza B viruses). Centers for Disease Control and Prevention, *Quadrivalent Influenza Vaccine* (last updated Dec. 14, 2017), https://www.cdc.gov/flu/protect/vaccine/quadrivalent.htm.

[35] Centers for Disease Control and Prevention, *How Influenza (Flu) Vaccines are Made* (last updated Nov. 7, 2016), https://www.cdc.gov/flu/protect/vaccine/how-fluvaccine-made.htm.

In 2003, FDA approved a nasal spray flu vaccine—called FluMist—that includes a live attenuated influenza vaccine for certain ages.[36] Because data from observational studies showed low effectiveness of FluMist Quadrivalent against a specific strain of the influenza virus in the United States during the 2013-2014 and 2015-2016 flu seasons, however, CDC's Advisory Committee on Immunization Practices (ACIP) did not recommend that the live attenuated vaccine be used by individuals for the past few years.[37] In February 2018, ACIP recommended that the live attenuated influenza vaccine be included on the 2018-2019 influenza vaccination schedule for individuals for whom it is appropriate.[38]

For the 2017-2018 flu season, manufacturers estimated that they would provide about 151 million to 166 million doses of injectable vaccine in the United States, and as of February 9, 2018, about 154.7 million doses of the seasonal influenza vaccine had been distributed.[39] About 119 million doses of the influenza vaccine were expected to be quadrivalent flu vaccine.[40] According to the CDC, about 15 to 20 percent of the supply of flu vaccine for the 2017-2018 flu season was manufactured through non-egg based manufacturing and about 80 to 85 percent was manufactured through the egg-based manufacturing process.[41]

ii. Seasonal Influenza Prevention and Vaccine Effectiveness

The primary method for preventing influenza is annual vaccination. According to the CDC's 2018 Congressional Budget Justification, vaccination prevented approximately 5.1 million influenza illnesses, 2.5 million influenza-associated medical visits, and 71,000 influenza-associated hospitalizations during the 2015-2016 influenza season.[42] Similarly, a 2015 study published in the journal *Vaccine* showed that the seasonal flu vaccine prevented more than 40,000 flu-associated deaths in the United States from 2005-2006 through 2013-2014.[43]

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[36] U.S. Food and Drug Administration, *FDA Information Regarding FluMist Quadrivalent Vaccine* (last updated Jan. 26, 2018), https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm508761.htm.
[37] Centers for Disease Control and Prevention, *Prevention and Control of Seasonal Influenza with Vaccines, Recommendations of the Advisory Committee on Immunization Practices—United States, 2016-17 Influenza Season* (Aug. 26, 2016), https://www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm#T1_down.
[38] Molly Walker, *ACIP Reinstates FluMist for 2018-2019 Flu Season*, MEDSCAPE (Feb. 21, 2018), https://www.medpagetoday.com/meetingcoverage/acip/71298.
[39] Centers for Disease Control and Prevention, *Seasonal Influenza Vaccine Supply & Distribution* (last updated Feb. 15, 2018), https://www.cdc.gov/flu/about/qa/index.htm. For the 2017-2018 season, 13 influenza vaccine products were approved by 6 different manufacturers. Out of these 13 influenza vaccine products, 9 were egg-based trivalent/quadrivalent inactive influenza vaccine (injectable), 2 were trivalent/quadrivalent recombinant hemagglutinin influenza vaccine (injectable), 1 was a cell culture-based vaccine quadrivalent inactivated influenza vaccine, and 1 was live attenuated influenza vaccine (CDC's Advisory Committee on Immunization Practices did not recommend use of this vaccine for the 2017-18 flu season). One of the nine egg-based trivalent/quadrivalent inactive influenza vaccines (injectable) was an adjuvanted trivalent inactivated influenza vaccine. Immunization Action Coalition, *supra* note 33.
[40] Centers for Disease Control and Prevention, *Quadrivalent Influenza Vaccine* (last updated Dec. 14, 2017), https://www.cdc.gov/flu/protect/vaccine/quadrivalent.htm.
[41] U.S. House of Representatives, Comm. on Energy and Commerce, Subcomm. on Oversight and Investigations, 115th Cong., Committee Staff Phone Briefing with the U.S. Dep't of Health and Human Services (Mar. 1, 2018).
[42] Centers for Disease Control and Prevention, *FY 2018 Congressional Budget Justification*, *supra* note 3, at 47.
[43] Ivo Foppa, et al., *Deaths averted by influenza vaccination in the U.S. during the seasons 2005/06 through 2013/14*, VACCINE Volume 33 (June 12, 2015), www.sciencedirect.com/science/article/pii/S0264410X15002315.

Likewise, according to a 2017 study published by the CDC in the journal *Pediatrics*, the influenza vaccine reduced the risk of flu-associated death by half for children with underlying high-risk medical conditions and by nearly two-thirds for healthy children.[44]

Indeed, research indicates that even if the flu vaccine fails to protect an individual against being infected with the flu, the vaccine may help reduce severe outcomes.[45] According to CDC estimates, approximately 80 percent of flu-associated deaths in children in past flu seasons have occurred in children who were not vaccinated.[46] Likewise, a 2017 study by the CDC showed that receiving the flu vaccine reduced severe outcomes in hospitalized patients by reducing deaths, reducing intensive care unit (ICU) admissions, reducing ICU length of stay, and reducing overall duration of hospitalization among hospital patients.[47] The study found that vaccinated adults were 52 to 70 percent less likely to die than unvaccinated flu-hospitalized patients and experienced additional benefits.[48]

CDC estimates the effectiveness of the flu vaccine every year, and by effectiveness, CDC means the rate at which the vaccine prevents a person from getting sick with the flu and going to the doctor (the effectiveness rate does not, however, account for other potential benefits from receiving the flu vaccine such as helping reduce severe outcomes if an individual gets the flu).[49] Recent studies show that seasonal flu vaccination typically has an effectiveness rate in the range of 40 to 60 percent.[50] According to CDC, the overall, adjusted vaccine effectiveness estimates for influenza seasons from 2005 to 2018 ranged from 10 to 60 percent.[51]

CDC's Adjusted Vaccine Effectiveness Estimates[52]

Year	Adjusted Overall Vaccine Effectiveness
2004-2005	10%
2005-2006	21%
2006-2007	52%
2007-2008	37%
2008-2009	41%

[44] Centers for Disease Control and Prevention, *CDC Study Finds Flu Vaccine Saves Children's Lives* (Apr. 3, 2017), https://www.cdc.gov/media/releases/2017/p0403-flu-vaccine.html.
[45] *Id*.
[46] Centers for Disease Control and Prevention, *Estimating Seasonal Influenza-Associated Deaths in the United States—Questions and Answers* (last updated Jan. 29, 2018), https://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm.
[47] Centers for Disease Control and Prevention, *New CDC Study Shows Flu Vaccine Reduces Severe Outcomes in Hospitalized Patients* (May 25, 2017).
[48] *Id*.
[49] Centers for Disease Control and Prevention, F*requently Asked Flu Questions 2017-2018 Influenza Season* (last updated Mar. 1, 2018), https://www.cdc.gov/flu/about/season/flu-season-2017-2018.htm.
[50] Centers for Disease Control and Prevention, *Vaccine Effectiveness—How Well Does the Flu Vaccine Work?* (last updated Oct. 3, 2017), https://www.cdc.gov/flu/about/qa/vaccineeffect.htm.
[51] Centers for Disease Control and Prevention, *Seasonal Influenza Vaccine Effectiveness, 2005-2018* (last updated Feb. 15, 2018), https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm.
[52] *Id*.

2009-2010	56%
2010-2011	60%
2011-2012	47%
2012-2013	49%
2013-2014	52%
2014-2015	19%
2015-2016	48%
2016-2017	40%
2017-2018	36%

Vaccine effectiveness can differ depending on the age of the individual that received the vaccination. For example, for the 2016-2017 flu season, the vaccine was 61 percent effective for individuals aged 6 months to 8 years, 19 percent effective for individuals aged 18 to 49 years, and 25 percent effective for people aged 65 years and older.[53] Similarly, preliminary data shows that the vaccine effectiveness for all virus types for the 2017-2018 flu season differed by age group—statistically significant protection was found among children aged 6 months through 8 years (a vaccine effectiveness rate of 59 percent was found) and adults aged 18 to 49 years old (a vaccine effectiveness rate of 33 percent was found).[54] CDC's analysis of the preliminary data did not find any statistically significant protection in other age groups.[55]

Moreover, vaccine effectiveness also differs across different subtypes of influenza. Research shows that the flu vaccine typically is more effective against influenza B and influenza A(H1N1) viruses than influenza A(H3N2) viruses.[56] Some researchers have raised concerns about the decline in effectiveness of the annual influenza vaccine, especially for the H3N2 virus.[57] A 2016 meta-analysis of 56 past studies published in PubMed and Embase found that, on average, the seasonal flu vaccine was 33 percent effective against the H3N2 virus, 54 percent effective against influenza B, 61 percent effective against the H1N1pdm09 virus, and 67 percent effective against H1N1.[58] During the 2017-2018 flu season in the United States, preliminary data shows that while the flu vaccine had an overall vaccine effectiveness rate of 36 percent, vaccine effectiveness for all ages was 25 percent against type A(H3N2) viruses, 67 percent against influenza A(H1N1)pdm09 viruses, and 42 percent effective against influenza B virus infection.[59]

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[53] Robert Lowes, *Flu Vaccine Efficacy Slips from Prior Estimate, CDC Says*, MEDSCAPE (June 23, 2017), https://www.medscape.com/viewarticle/882075.
[54] Centers for Disease Control and Prevention, *Interim Estimates of 2017-18 Seasonal Influenza Vaccine Effectiveness – United States, February 2018* (Feb. 16, 2018), https://www.cdc.gov/mmwr/volumes/67/wr/mm6706a2.htm#contribAff.
[55] *Id*.
[56] Centers for Disease Control and Prevention, *Vaccine Effectiveness—How Well Does the Flu Vaccine Work?* (last updated Oct. 3, 2017), https://www.cdc.gov/flu/about/qa/vaccineeffect.htm.
[57] Nicholas C. Wu, *A structural explanation for the low effectiveness of the seasonal influenza H3N2 vaccine*, PLOS PATHOGENS (Oct. 23, 2017), http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006682.
[58] Edward A. Belongia, et al., *Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies*, THE LANCET Volume 16 (Aug. 2016); *See also* Sarah Zhang, *Scientists Found a Flu Vaccine – Now They Have to Fix It*, WIRED (Oct. 9, 2015), http://www.wired.com/2015/10/scientists-pinpoint-flu-vaccine-flaw-h3n2/.
[59] Centers for Disease Control and Prevention, *Interim Estimates of 2017-18 Seasonal Influenza Vaccine Effectiveness – United States, February 2018*, *supra* note 55.

There are many different factors that may contribute to reduced vaccine effectiveness for the influenza, including but not limited to: (1) antigenic differences between the circulating strain and the strain used to create the vaccine caused by antigenic drift and antigenic shift; (2) egg adaptation; and (3) other factors such as immune history[60] and some individuals potentially requiring a higher amount of certain antigens, such as H3N2, to elicit a proper immune response to that particular strain of the influenza. The protective benefit from receiving the flu vaccine typically is decreased if the primary circulating influenza viruses are different from the viruses that were used to make the vaccine for that season.[61] As previously mentioned, influenza viruses are continuously changing through antigenic drift and antigenic shift, and these changes can therefore impact the efficacy of the seasonal flu vaccine if the majority of the circulating viruses become different than those used for the vaccine. Even if antigenic drift occurs, however, the vaccine may provide protective benefit if the circulating influenza virus is only mildly or moderately different than the virus used for the vaccine. If the small genetic changes that occur through antigenic drift accumulate over time and result in a virus that looks different to a person's immune system, the antibodies created against older viruses may no longer recognize the "newer" virus, and the person may no longer be protected.[62]

While vaccine effectiveness is generally interpreted in the context of vaccine match/mismatch to circulating strains that have mutated to explain reduced protection, egg adaptation may also contribute to lower effectiveness of the vaccine—especially for certain strains of the virus such as H3N2.[63] More specifically, as human influenza viruses adapt to grow in eggs during the manufacturing process, genetic changes may occur in the viruses referred to as "egg-adapted changes."[64] These egg-adapted changes can have important consequences for an individual's immune response to vaccination such as causing an individual to produce antibodies that are less effective at preventing illness caused by the specific flu viruses in circulation.[65] 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.[66] Likewise, for the 2017-2018 flu season, some experts have expressed concern that the flu vaccine's reduced effectiveness against

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[60] A recent study found that immune history with the influenza influences an individual's response to the flu vaccine. Matt Wood, *Immune history influences effectiveness of flu vaccine, study finds*, UCHICAGONEWS (Feb. 20, 2018), https://news.uchicago.edu/article/2018/02/20/immune-history-influences-effectiveness-flu-vaccine-study-finds.

[61] Centers for Disease Control and Prevention, *Flu Vaccine Effectiveness: Questions and Answers for Health Professionals* (last updated Jan. 29, 2016), https://www.cdc.gov/flu/professionals/vaccination/effectivenessqa.htm.

[62] Centers for Disease Control and Prevention, *How the Flu Virus Can Change: "Drift" and "Shift,"* (last updated Sept. 27, 2017), https://www.cdc.gov/flu/about/viruses/change.htm.

[63] Nicholas C. Wu, *supra* note 58.

[64] Centers for Disease Control and Prevention, *Antigenic Characterization* (last updated Sept. 27, 2017), *available at* https://www.cdc.gov/flu/professionals/laboratory/antigenic.htm.

[65] Centers for Disease Control and Prevention, *Cell-Based Flu Vaccines* (last updated Nov. 7, 2016), https://www.cdc.gov/flu/protect/vaccine/cell-based.htm.

[66] Danuta 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 (Mar. 25, 2014), http://journals.plos.org/plos.org/plosone/article?id=10.1371/journal.pone0092153.

H3N2 may be caused in part by egg adaptation.[67] According to a February 15, 2018 statement by FDA Commissioner Scott Gottlieb, M.D., the commonly used egg-based manufacturing process may not have produced a vaccine that was as effective against H3N2 as the cell-based manufacturing process:

> A preliminary analysis of CMS data indicates that this year, the cell-based influenza vaccine appears to have somewhat better effectiveness in preventing influenza than the egg-based vaccine. Scientists at the FDA, CDC, and NIH are working diligently to fully understand the basis for this finding, so that all of next year's vaccines can provide better protection in preventing the flu. Better understanding why the cell-based vaccine offered better protection against H3N2 this season, when compared to the egg-based vaccine, may offer important clues to help improve the production of a more effective H3N2 vaccine for next season.[68]

Similarly, CDC also recently said "we're hoping this year to find out whether or not there's a performance difference between cell-based vaccines and the egg-based vaccines."[69]

More recently, on February 26, 2018, Dr. Gottlieb indicated that the FDA did not believe that the reduced effectiveness of the 2017-2018 seasonal vaccine against H3N2 was caused by public health authorities choosing the wrong strain of H3N2 when starting the process of making the 2017-2018 seasonal influenza vaccine. Dr. Gottlieb stated that "so far the data we have suggests that the viruses provided by reference laboratories to manufacturers to make this year's vaccines do reasonably match the circulating flu strains that are causing most of the illnesses."[70] Dr. Gottlieb provided several reasons that might explain the limited effectiveness of the 2017-2018 seasonal influenza vaccine against H3N2:

> One theory is that people might require a higher amount of H3N2 antigen to elicit a proper immune response to that particular strain of influenza. As I noted previously, the work conducted with CMS shows a preliminary finding that suggests the cell-based influenza vaccine might be somewhat more effective than the egg-based vaccine. We are working to follow up on that finding. We're also combing through the data to see if there are other reasons for why this season's vaccines were less effective against H3N2.[71]

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[67] Lisa Schnirring, University of Minnesota, Center for Infectious Disease Research and Policy, *WHO changes 2 strains for 2018-19 flu vaccine* (Feb. 22, 2018), http://www.cidrap.umn.edu/news-perspective/2018/02/who-changes-2-strains-2018-19-flu-vaccine.

[68] U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D. on the efficacy of the 2017-2018 influenza vaccine* (Feb. 15, 2018), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm597077.htm.

[69] Maggie Fox, *Why next year's flu vaccine will be lousy, too*, NBC NEWS (Feb. 23, 2018), https://www.nbcnews.com/health/health-news/why-next-year-s-flu-vaccine-will-be-lousy-too-n850641.

[70] U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA's ongoing efforts to help improve effectiveness of influenza vaccines* (Feb. 26, 2018), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm598317.htm.

[71] *Id.*

The FDA anticipates that by better understanding why the effectiveness of the influenza vaccine tends to be lower against H3N2, FDA can hopefully enhance vaccine effectiveness.

iii. Vaccine Coverage

Since 2010, ACIP has recommended annual vaccinations for everyone aged 6 months or older.[72] From the 2010-2011 to 2016-2017 flu seasons, an average of 56.5 percent of children (aged 6 months to 17 years) and 41.7 percent of adults were vaccinated each year.[73] Data from the 2015-2016 season showed that 59.3 percent of children and 41.7 percent of adults were vaccinated.[74] For 2016-2017 season, 59 percent of children and 43.3 percent of adults were vaccinated.[75] The estimate for this season, as of November 2017, was that 38.6 percent of all persons 6 months and older received the flu vaccine (this early estimate of flu season vaccination coverage is similar to coverage at the same time last flu season for all persons 6 months and older).[76]

The Department of Health and Human Services (HHS) supports efforts to increase annual vaccination and continuously engages in efforts to improve public awareness and provider knowledge about influenza and the importance of vaccination.[77] As part of the Healthy People 2020 initiative, HHS has set a goal for states to vaccinate 70 percent of their population. 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.

D. Development of a Universal Flu Vaccine

One long-term goal to improve preparedness for and response to the influenza is to develop a universal vaccine that would provide long-lasting immunity against multiple strains of the influenza. The goal is to eliminate the need for individuals to receive an annual seasonal flu vaccine and to provide protection against newly emerging flu strains. The Biomedical Advanced Research and Development Authority (BARDA) within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services is coordinating a broad-interagency partnership to support the development of improved influenza vaccines, including a universal flu vaccine.[78] In June 2017, the National Institute of Allergy and Infectious Disease (NIAID) held a workshop entitled "Pathway to a Universal Influenza Vaccine" to identify and develop criteria that would define a universal influenza vaccine, discuss knowledge gaps in the search for this vaccine, and to identify research strategies to address these

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[72] Centers for Disease Control and Prevention, *FY 2018 Congressional Budget Justification*, *supra* note 3, at 18.
[73] Centers for Disease Control and Prevention, *Flu Vaccination Coverage, United States, 2016-17 Influenza Season* (last updated Sept. 28, 2017), https://www.cdc.gov/flu/fluvaxview/coverage-1617estimates.htm.
[74] *Id*.
[75] *Id*.
[76] Centers for Disease Control and Prevention, *National Early-Season Flu Vaccination Coverage, United States, November 2017* (last updated Dec. 9, 2016), https://www.cdc.gov/flu/fluvaxview/nifs-estimates-nov2017.htm.
[77] Centers for Disease Control and Prevention, *FY 2018 Congressional Justification*, *supra* note 3, at 46.
[78] Centers for Disease Control and Prevention, *Influenza Vaccine Advances—Questions and Answers* (last updated Sept. 28, 2016), https://www.cdc.gov/flu/about/qa/advances.htm.

gaps.[79] Following the workshop, NIAID published a strategic plan in February 2018 to "reinvigorate pursuit of a universal influenza vaccine."[80]

E. Pandemic Influenza

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. According to CDC, pandemics rarely occur and past pandemics include the 2009 Pandemic (H1N1 virus), the 1968 Pandemic (H3N2 virus), the 1957-1958 Pandemic (H2N2 virus), and the 1918 Pandemic (H1N1 virus).[81]

HHS maintains a *Pandemic Influenza Plan* that was developed in 2005.[82] The Committee wrote to HHS in April 2017 asking about the status of the updated plan.[83] HHS subsequently released the updated plan in June 2017.[84] The *Pandemic Influenza Plan* acts "as a blueprint for all HHS pandemic influenza preparedness planning and response activities."[85] In the 2017 update, HHS notes that one of the improvements in the agency's preparedness and response activities for pandemic influenza over the past decade is that "HHS efforts in pandemic influenza preparedness now are closely aligned with seasonal influenza activities, harnessing expanded surveillance, laboratory, vaccine, and antiviral drug resistance monitoring capacity."[86] According to the 2017 update:

> [T]he continually changing nature of influenza viruses that can lead to mismatches between vaccine strains and circulating viruses, as seen during the 2014-2015 influenza season, remind us that pandemic and seasonal influenza planning and improvement efforts are interdependent. Both rely on a strong and sustainable public health system infrastructure that can rapidly detect, and respond to, changes in circulating influenza viruses. Many of the activities that HHS and its partners

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[79] National Institutes of Health, National Institute of Allergy and Infectious Disease, *Experts Outline Pathway to a Universal Influenza Vaccine* (Oct. 17, 2017), https://www.niaid.nih.gov/news-events/experts-outline-pathway-universal-influenza-vaccine.

[80] Emily J. Erbelding, et al., *A Universal Influenza Vaccine: The Strategic Plan for the National Institute of Allergy and Infectious Diseases* (Mar. 2018).

[81] Centers for Disease Control and Prevention, *Past Pandemics* (last updated Nov. 2, 2017), https://www.cdc.gov/flu/pandemic-resources/basics/past-pandemics.html.

[82] Centers for Disease Control and Prevention, *National Pandemic Influenza Plans* (last updated Jun. 22, 2017), https://www.cdc.gov/flu/pandemic-resources/planning-preparedness/national-strategy-planning.html.

[83] Letter from the Hon. Greg Walden, Chairman, H. Comm. on Energy & Commerce, *et al.*, to Hon. Thomas Price, M.D., Sec'y, U.S. Dep't of Health & Human Services (Apr. 20, 2017), *https://archives-energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/documents/20170420HHS.pdf.* In response to Questions for the Record from the Subcommittee's November 2015 hearing on seasonal influenza, HHS told the Committee that it expected to release the updated plan by the end of 2016. *Id.*

[84] Centers for Disease Control and Prevention, *National Pandemic Influenza Plans* (last updated Jun. 22, 2017), https://www.cdc.gov/flu/pandemic-resources/planning-preparedness/national-strategy-planning.html.

[85] U.S. Dep't of Health & Human Serv., *HHS Pandemic Influenza Plan*, at 2 (Nov. 2005), http://www.flu.gov/planning-preparedness/federal/hhspandemicinfluenzaplan.pdf.

[86] U.S. Dep't of Health and Human Services, *Pandemic Influenza Plan, 2017* Update (Jun. 2017), https://www.cdc.gov/flu/pandemic-resources/pdf/pan-flu-report-2017v2.pdf.

undertake each year to understand and mitigate the impact of seasonal influenza are critical to a pandemic response both domestically and globally.[87]

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

After the 2014-2015 vaccine mismatch, then HHS Secretary Sylvia Burwell, through her counselors, requested that HHS experts recommend actions to mitigate the seasonal influenza mismatch problem. On May 6, 2015, a memorandum of influenza process improvements was sent to Secretary Burwell. In November 2015, 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. On November 19, 2015, the Subcommittee held a hearing on whether the public health response to seasonal influenza had improved.[88] The Subcommittee will follow-up on the status of HHS actions.

Among the key actions taken to improve seasonal flu preparedness and examined at the hearing were:

- *Technological improvements*. Vaccine manufacturers were in the process of adopting several process improvements for pandemic vaccine. HHS anticipated asking 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, was 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 that circumstances under which 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

[87] *Id*. at 10.
[88] Hearing before the U.S. House of Reps., Energy and Commerce Subcommittee on Oversight and Investigations, "U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?" (Nov. 19, 2015).

a drift of the H1N1 strain.[89] Approximately 7 million doses of the 1986 monovalent vaccine were manufactured or distributed late in 1986.[90]

- *Late season change to tri- or quadrivalent vaccine.* HHS had 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 had been implemented, and FDA had done likewise with the Chair of its Vaccines and Related Biological Products Advisory.

IV. Issues

The following issues may be examined at the hearing:

- How has public health preparedness for the seasonal influenza improved in recent years?

- What challenges do public health authorities face when developing the seasonal influenza vaccine?

- How can better and more effective influenza vaccines be manufactured? Are there concerns with the egg-based manufacturing process?

- What guidance would be effective in helping increase the use of antiviral medications and reduce the use of antibiotics in the treatment for influenza? Do we need more treatments for the flu?

V. Staff Contacts

If you have any questions regarding the hearing, please contact Natalie Turner, Alan Slobodin, or Jen Barblan of the Committee staff at (202) 225-2927.

[89] 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).
[90] Centers for Disease Control and Prevention, 37 CDC Morbidity and Mortality Weekly Report 469 (Aug. 12, 1988).