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ONE HUNDRED FOURTEENTH CONGRESS

Congress of the United States
House of Representatives
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To: Subcommittee on Oversight and Investigations Democratic Members and Staff

Fr: Committee on Energy and Commerce Democratic Staff

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

On Thursday, November 19, 2015, at 10:00 a.m. in room 2322 of the Rayburn House Office Building, the Subcommittee on Oversight and Investigations will hold a hearing titled "U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?" The hearing will focus on the public health response to seasonal influenza, in particular the efficacy of flu vaccines. The hearing will also explore whether advances in science and technology could be used to strengthen the federal response in the future.

I. BACKGROUND

Influenza is "a contagious respiratory illness caused by influenza viruses that infect the nose, throat, and lungs."[1] While typical symptoms include fever, cough, or sore throat, complications from the flu can lead to severe illnesses like bacterial pneumonia or even cause death. Children younger than age five, adults sixty-five years of age and older, pregnant women, residents of nursing homes and long-term care facilities, and others with medical conditions (e.g., weakened immune systems or heart disease) are at a higher risk for developing flu-related complications.[2]

The timing and duration of flu seasons vary but can begin in October and last as late as

[1] Centers for Disease Control and Prevention, *Key Facts About Influenza (Flu) and Flu Vaccine* (online at www.cdc.gov/flu/keyfacts.htm).

[2] Centers for Disease Control and Prevention, *People at High Risk of Developing Flu-Related Complications* (online at www.cdc.gov/flu/about/disease/high_risk.htm).

May. Peak activity generally occurs in January and February.[3] The severity of flu seasons are extremely unpredictable: "between 1976 and 2007, estimates of flu-associated deaths in the United States [ranged] from a low of about 3,000 to a high of about 49,000 people."

Flu vaccines protect individuals against the flu by causing protective antibodies to develop in the body.[4] Traditional flu vaccines, called "trivalent" vaccines, are made to protect against three viruses: two influenza A viruses (an H1N1 and an H3N2 strain) and an influenza B virus. A quadrivalent vaccine, which protects against two influenza A viruses and two influenza B viruses, is also available. The Centers for Disease Control and Prevention (CDC) recommends that everyone six months of age and older receive a flu vaccine each year. CDC also recommends use of antiviral drugs for those who do become infected to reduce the length and severity of symptoms.[5]

Because different strains of the flu can predominate in any given year, the flu vaccine must be modified annually.[6] At the beginning of each calendar year, the Food and Drug Administration (FDA) and the World Health Organization (WHO) review data to recommend the composition of influenza virus vaccines for the next winter. The FDA then convenes its Vaccine and Related Biological Products Advisory Committee and recommends strains for both the trivalent and quadrivalent vaccines. The viruses are then adapted for use in manufacturing the seasonal vaccine, which begins shipping at the end of the summer. Throughout the year, the WHO monitors worldwide influenza disease.

Because of the time required to produce and distribute influenza vaccines, decisions regarding which strains to incorporate into annual seasonal influenza vaccines must be made approximately eight months before the onset of the influenza season. During this time, influenza viruses will change genetically, a process known as "antigenic drift." Occasionally, the antigenic drift is so significant that it results in influenza vaccines that are a poor match for the predominant virus circulating in the population. This occurred in the 2014-2015 flu season, in which the seasonal flu vaccine was only 23 percent effective, meaning it reduced a person's risk of having to go a doctor because of the flu by 23 percent.[7]

Since the CDC began monitoring effectiveness on a widespread scale in 2009, vaccines

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[3] *Id.*

[4] Centers for Disease Control and Prevention, *Key Facts About Seasonal Flu Vaccine* (online at www.cdc.gov/flu/protect/keyfacts.htm).

[5] Centers for Disease Control and Prevention, *What You Should Know About Flu Antiviral Drugs* (online at www.cdc.gov/flu/antivirals/whatyoushould.htm).

[6] Food and Drug Administration, *Vaccines and Related Biological Products Advisory Committee* (online at www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/).

[7] Centers for Disease Control and Prevention, *Protection from Flu Vaccine Reduced This Season* (Jan. 15, 2015) (press release).

have typically shown approximately 50 to 60 percent effectiveness.[8] CDC continues to recommend vaccinations during drifted seasons, as flu vaccines protect against three or four different strains of influenza, all of which may circulate over the season. Additionally, antibodies created through vaccination with one influenza virus can sometimes offer protection against drifted influenza viruses, thus potentially reducing illnesses, doctor's visits, hospitalizations, and deaths.

For the 2015-2016 flu season, the FDA Vaccine and Related Biological Products Advisory Committee met on March 4, 2015, to select the flu strains for this year's vaccine.[9] Seven manufacturers are producing vaccines: GlaxoSmithKline, Sanofi Pasteur, Novartis, CSL Limited, Protein Sciences Corp., ID Biomedical Corp., and MedImmune. The manufacturers have projected they will provide between 171 to 179 million doses of vaccine for the U.S. market.[10]

It is still too early in the year to determine the severity and length of the 2015-2016 flu season and the effectiveness of the vaccine.[11] However, the most recent CDC report indicates that all of the influenza viruses collected and analyzed from around the world have been characterized antigenically and/or genetically as being similar to the influenza vaccine viruses recommended for inclusion in the 2015-2016 Northern Hemisphere vaccine.[12] This suggests that the 2015-2016 flu vaccine will likely be more effective than last year's vaccine.[13]

II. VACCINE DEVELOPMENT: ALTERNATIVE TECHNOLOGIES

HHS is undertaking a number of efforts to improve influenza vaccine development and the manufacturing process. These include activities to improve global surveillance and detect new emergent strains more quickly; to incorporate technological improvements to speed production and regulatory timelines; to make more effective vaccines to provide better protection against drifted virus strains; and to improve systems for distribution, administration, and monitoring of vaccines.

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[8] Centers for Disease Control and Prevention, *Seasonal Influenza Vaccine Effectiveness, 2005-2015* (online at www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm).

[9] Food and Drug Administration, *Influenza Virus Vaccine for the 2015-2016 Season* (online at www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm454877.htm).

[10] Centers for Disease Control and Prevention, *Seasonal Influenza Vaccine & Total Doses Distributed* (Nov. 4, 2015) (online at www.cdc.gov/flu/professionals/vaccination/vaccinesupply.htm).

[11] Centers for Disease Control and Prevention, *What You Should Know for the 2015-2016 Influenza Season* (Oct. 20, 2015) (online at www.cdc.gov/flu/about/season/flu-season-2015-2016.htm).

[12] *Id.*

[13] *This Year's Flu Vaccine Should Be Better Match: CDC*, HealthDay (Sept. 17, 2015) (online at www.nlm.nih.gov/medlineplus/news/fullstory_154680.html).

Traditional vaccine development uses egg-based technology, which involves a lengthy manufacturing process. In egg-based manufacturing, each virus strain is injected into eggs, which are then incubated. Once the viruses multiply, the fluid from the eggs is harvested, purified, and tested for potency and safety.[14]

Several new technologies have been developed in recent years to improve the manufacturing of flu vaccines, including cell-based vaccines, recombinant vaccines, and adjuvants. Cell-based technology uses cells infected with the influenza virus instead of fertilized eggs.[15] This technology makes for faster start-up of vaccine manufacturing, but it requires that an adequate supply of cells is readily available for production. In November 2012, the FDA approved Novartis' Flucelvax, the first vaccine using cell culture technology for individuals 18 and older.

Recombinant technology uses a similar technique, but uses specific proteins or genes from the virus instead of the entire virus as the antigen.[16] While vaccines produced using this technology have a shorter shelf life, their manufacturing process is more truncated than the process for egg-based vaccines. These shorter timelines allow recombinant-based vaccines to be produced more quickly in the event of a pandemic or vaccine supply shortage. In January 2013, the FDA first approved Flublok made by Protein Sciences Corporation for individuals 18 or older. It is particularly recommended for those with egg allergies.

An adjuvant is an "antigen-sparing technology" that is added to a vaccine to enhance immune response.[17] Adjuvants can be added to vaccines made with different production methods, including egg-based, cell-based, or recombinant technology. Currently, there are no seasonal flu vaccine adjuvants approved for use in the United States, but the technology has been used in pandemic influenza vaccines, and many labs at NIH's National Institute of Allergy and Infectious Disease (NIAID) are currently engaged in adjuvant research.

Scientists are also seeking to develop a universal influenza vaccine to protect against all flu strains.[18] Though there is promising data to support this idea, a universal vaccine is considered at least five to seven years away.

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[14] Food and Drug Administration, *The Evolution, and Revolution, of Flu Vaccines* (online at www.fda.gov/ForConsumers/ConsumerUpdates/ucm336267.htm).

[15] Centers for Disease Control and Prevention, *Cell-Based Flu Vaccines* (online at www.cdc.gov/flu/protect/vaccine/cell-based.htm).

[16] Centers for Disease Control and Prevention, *Flublok Seasonal Influenza (Flu) Vaccine* (online at www.cdc.gov/flu/protect/vaccine/qa_flublok-vaccine.htm).

[17] NIH National Institute of Allergy and Infectious Disease, *Vaccine Adjuvants* (online at www.niaid.nih.gov/topics/Adjuvants/Understanding/Pages/WhatIs.aspx).

[18] *A Universal Flu Vaccine May Be On the Horizon*, Smithsonian Magazine (Jan. 26, 2015) (online at www.smithsonianmag.com/science-nature/measles-vaccine-universal-flu-influenza-cdc-disease-outbreak-180954020/?no-ist).

III. AGENCY RESPONSIBILITIES

CDC operates the U.S. seasonal flu surveillance systems, which track trends in the rate of illness and hospitalization.[19] CDC also monitors the types and subtypes of circulating flu viruses, the emergence of new strains, and the geographic spread of the flu virus. Additionally, CDC administers two programs that provide vaccines to uninsured and underinsured children, adolescents, and adults and invest in the infrastructure necessary to reach these populations (the Vaccines for Children and Section 317 programs).[20] Finally, CDC maintains the Strategic National Stockpile (SNS), the nation's repository of flu vaccines and other critical pharmaceutical products and medical supplies for use during a public health emergency.

FDA is "responsible for the licensure and regulation of influenza vaccine — including the approval of facilities in which influenza vaccine is produced — for the U.S. market."[21] FDA issues guidance, consults with manufacturers, and regulates the vaccine's production and use. FDA also reviews and approves the composition of the seasonal vaccine annually, through the Vaccine and Related Biological Products Advisory Committee.[22]

The Biomedical Advanced Research and Development Authority (BARDA), located within HHS, contracts with vaccine manufacturers for advanced research and development for vaccine technologies to respond to public health emergencies.[23] BARDA's investments in cell and recombinant vaccine manufacturing have led to the FDA licensure of vaccines using these technologies.

NIAID conducts research to prevent, diagnose, and treat seasonal and pandemic influenza.[24] NIAID's long-standing influenza research program supports research on the

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[19] Centers for Disease Control and Prevention, *Overview of Influenza Surveillance in the United States* (online at www.cdc.gov/flu/weekly/overview.htm).

[20] Centers for Disease Control and Prevention, *Justification of Estimates for Appropriations Committees* (Fiscal Year 2015) (online at www.cdc.gov/fmo/topic/Budget%20Information/appropriations_budget_form_pdf/FY2015_CJ_CDC_FINAL.pdf).

[21] Government Accountability Office, *Influenza Vaccine: Federal Investments in Alternative Technologies and Challenges to Development and Licensure* (June 2011) (GAO-11- 435).

[22] Food and Drug Administration, *Vaccines and Related Biological Products Advisory Committee* (online at www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/).

[23] Office of the Assistant Secretary for Preparedness and Response, U.S. Department of Health and Human Services, *Influenza Division* (online at www.phe.gov/about/barda/Pages/influenza.aspx).

[24] NIH National Institute of Allergy and Infectious Diseases, *NIAID Role in Influenza Research* (online at www.niaid.nih.gov/topics/flu/Pages/default.aspx).

effectiveness of influenza vaccines, such as adjuvant technologies, and the development of a universal vaccine candidate.

IV. WITNESSES

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