Committee on Energy and Commerce
Subcommittee on Oversight and Investigations

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

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The Honorable Jan Schakowsky (D-IL)

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

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

Response:

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

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

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

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

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

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

The Honorable Brett Guthrie (R-KY)

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

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

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

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

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

Response

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

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

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

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

Response:

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

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

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

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

The Honorable Susan Brooks (R-IN)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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