Dr. Robert R. Redfield  
Director  
Centers for Disease Control and Prevention  
Atlanta, GA 30329

Dear Dr. Redfield,

We write to request information from the Centers for Disease Control and Prevention (CDC) on how the agency plans to improve seasonal influenza vaccine coverage generally for seniors, and further, on whether a preferential recommendation from the CDC Advisory Committee on Immunization Practices (ACIP) for vaccinating adults 65 years of age and older (seniors) with a high-dose (Fluzone HD) or an adjuvanted (FLUAD) influenza vaccine could reduce deaths and hospitalizations or even improve vaccination coverage. These two vaccines are of interest because there seems to be substantial evidence of superior effectiveness compared to the standard dose vaccine, and at least one respected foreign public health authority has recently issued a preferential recommendation for each of these products.

Need to improve flu vaccination rates for seniors

The need for action to reduce flu-related deaths and hospitalizations is urgent, especially when the A (H3N2) flu strain is predominant. More people were killed by seasonal influenza in last winter’s severe flu season than in any other since 1976, with an estimated 78,000 deaths. For the 2017-2018 influenza season, CDC estimated that adults aged 65 years and older accounted for 90 percent of total influenza-associated deaths, or an estimated 68,448 deaths. Our senior citizens, adults aged 65 and older, disproportionately bear the burden of infection.

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1 According to the CDC, it was the deadliest season since 1976, the date of the first published paper reporting total seasonal flu deaths. Susan Sculli, *Flu season deaths top 80,000 last year, CDC says*, CNN (Sept. 27, 2018), https://www.cnn.com/2018/09/26/health/flu-deaths-2017-2018-cdc-bn/index.html.

hospitalizations, and death. It has been recognized for years that seniors are at greater risk of serious complications from the flu because human immune defenses become weaker with age.

Although studies have indicated significantly lower effectiveness rates for flu vaccines in seniors than the rates for other subpopulations, those who get the flu after receiving a vaccine are less likely to require hospitalization and they are less likely to die. Moreover, a recent study showed a significant association between a decline in flu vaccination coverage and a rise in flu-like illness rates.

Vaccination rates for seniors have remained flat throughout the last two decades.

Flu vaccination has been shown to reduce the risk of flu illness and the risk of serious flu outcomes, such as hospitalization and death. While vaccination rates for seniors are relatively higher than for other age groups, unfortunately, the vaccination rate for seniors has plateaued at around the 60-65 percent range for about two decades, and slightly declined last season to 59 percent.

Effectiveness of a high-dose or adjuvanted flu vaccine for seniors as compared to a standard dose flu vaccine

Two Food and Drug Administration (FDA)-approved vaccines, Fluzone HD and FLUAD, are available as alternatives to standard-dose vaccines. There appears to be substantial evidence substantiating superior effectiveness for seniors with each of these alternatives compared to the standard dose flu vaccine. In addition, each alternative has received a preferential recommendation for use in the senior population from at least one respected foreign public health authority.

Fluzone HD, a high-dose flu vaccine which targets those over age 65 years, was approved by the FDA in 2009 and became available in the U.S. for the 2010-2011 flu season. This vaccine, manufactured by Sanofi, contains four times more antigen (the part of the vaccine that prompts the body to make antibody) than other flu vaccines and is supposed to stimulate a stronger immune response that will produce more antibodies and, theoretically, give the elderly better protection from getting sick with influenza. The CDC included the vaccine in the 2010-

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7 Letter from Center for Biologics Evaluation and Research, FDA, to Sanofi Pasteur Inc. (Dec. 23, 2009) (on file with Committee).
11 recommendations for use in persons 65 years of age and older. As stated in CDC’s responses to Questions for the Record from the February 3, 2015 hearing before the Subcommittee on Oversight and Investigations, “ACIP is reviewing the evidence for Fluzone HD and could consider preferential language. Note that ACIP recommendations already state that Fluzone HD has been found to be more effective than standard dose vaccine in one study.” Indeed, several studies since February 2015 have found superior effectiveness in different contexts along with a randomized clinical trial.9 Four years later, CDC ACIP still has not issued preferential language even though there have been additional studies confirming Fluzone HD is more effective than standard dose vaccine for seniors.

In May 2018, Canada’s National Advisory Committee on Immunization (NACI) issued a preferential recommendation10 for Fluzone HD after only two years of the vaccine’s availability on the Canadian market. In contrast, although the FDA approved Fluzone HD for use in the U.S. in 2009 with about a decade of experience, CDC ACIP has not issued a preferential recommendation.

CDC’s testimony at the March 8, 2018 Subcommittee on Oversight and Investigations hearing implied that a preferential recommendation was not made for Fluzone HD since Fluzone HD’s market share has been increasing anyway without the preferential recommendation.11 If this is the case, we would be interested in what market information the CDC ACIP uses to make

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9 See, e.g., S.G. Robison and A.R. Thomas, Assessing the effectiveness of high-dose influenza vaccine in preventing hospitalization among seniors, and observations on the limitations of the effectiveness study design, 36 Vaccine 6683 (Oct. 29, 2018) (Oregon Health Authority study of more than 144,000 seniors found high-dose influenza vaccine was 30.7 percent more effective for seniors in preventing influenza-related hospitalization); Hector S. Izurieta, et al, Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis, 15 The Lancet 293 (Mar. 2015) (According to a study done by researchers at the FDA, CDC and Centers for Medicare and Medicaid Services, people who received the high-dose flu vaccine during the 2012-2013 flu season were 36.4 percent less likely to die compared to the standard-dose vaccine when the A(H3N2) influenza viruses were broadly circulating); Joshua Doyle, et al, Relative Effectiveness of High-Dose and Standard-Dose Influenza Vaccine Against Influenza-Related Hospitalization Among Older Adults – United States, 2015-2017 (Oct. 4, 2018) (According to a study by CDC and academic researchers, comparison of high-dose versus standard-dose vaccine effectiveness during two recent influenza seasons (one H1N1 and one H3N2-predominant) suggested relative benefit (non-significant) of high-dose influenza vaccine in protecting against flu-associated hospitalization among persons aged 65 years and older); Yinong Young-Xu, et al, Clinical Effectiveness of High-Dose Trivalent versus Quadrivalent Influenza Vaccination among Veterans Health Administration Patients (Oct. 5, 2018) available at https://idsa.confex.com/idsa/2018/webprogram/Paper71620.html (According to a study of 782,346 VHA patients by researchers from Veterans Affairs Medical Center and Dartmouth School of Medicine, high-dose trivalent vaccine was more than effective than standard-dose vaccination in preventing flu-related hospitalizations).

10 "At an individual level, NACI recommends that high-dose TIV [trivalent influenza vaccine] [referring to Fluzone HD] should be offered over standard-dose TIV to persons 65 years of age and older. NACI concludes that, given the burden of disease associated with influenza A (H3N2) and the good evidence of better efficacy compared to standard-dose TIV in this age group, high-dose TIV should be offered over standard-dose TIV to persons 65 years of age and older (Grade A).” An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI), Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2018-2019 (May 2018).

11 H. Comm. on Energy and Commerce, Subcomm. on Oversight and Investigations, hearing on “Examining Public Health Preparedness for and Response Efforts to Seasonal Influenza,” Mar. 8, 2018, Testimony of Dr. Anne Schuchat, Preliminary transcript 79 (“We have the market of the higher dose product has been increasing since it became available.”).
such a determination, as well as the basis for its assumption that this market share would continue to increase, and would increase at the same rate.

In addition, CDC’s testimony implied a potential concern that there might be insufficient availability of Fluzone HD to support a preferential recommendation, and frustrated patients upon learning from their provider that Fluzone HD was not available would go unvaccinated. If this is the case, however, it is unknown why the CDC ACIP would assume Sanofi’s manufacturing capacity for greater availability of Fluzone HD doses may be limited. This assumption seems questionable since Sanofi currently manufactures 53 million total doses of flu vaccine, and recently opened a third manufacturing facility. It is also unclear why the CDC ACIP would believe that Sanofi would be unable to shift and/or increase its manufacturing capacity to support a preferential recommendation.

FLUAD, which was approved by the FDA in November 2015, is a standard-dose, three-component (trivalent) inactivated flu vaccine that contains the adjuvant MF59. An adjuvant is an ingredient added to a vaccine that helps create a stronger immune response to vaccination. It is the only adjuvanted flu vaccine in the U.S., and it is manufactured by Seqirus.

While there have been no randomized trials of relative efficacy of FLUAD against laboratory-confirmed flu in seniors, there are several studies that have compared the effectiveness of FLUAD with standard unadjuvanted flu vaccines. FLUAD has been preferentially recommended by the United Kingdom, Austria, Italy (75 years of age and older), and regions in Spain. CDC ACIP has not issued a preferential recommendation for FLUAD.

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12 Id. at 79-80 (“One of the things we found is that the vaccine that they have at the doctors’ office or the pharmacy is the one that you should get because there may not be the other product if you’re looking for it.”).

13 There are about 51 million seniors in the U.S.

14 See, e.g., Salvatore Mannino, et al, Effectiveness of Adjuvanted Influenza Vaccination in Elderly Subjects in Northern Italy, 176 American Journal of Epidemiology 527 (September 15, 2012) (Vaccination with MF59 adjuvanted trivalent inactivated vaccine reduced the risk of hospitalization for influenza or pneumonia in the elderly during the peak of the influenza season by 25 percent relative to vaccination with nonadjuvanted trivalent inactivated vaccine). Alexander Domnich, et al, Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: A systematic review and meta-analysis, 35 Vaccine 513 (January 23, 2017) (Available evidence suggests that MF59 adjuvanted flu vaccine is effective in “real world” conditions, especially in preventing hospitalizations for various influenza complications, and is superior to conventional non-adjuvanted vaccines); S. Gravenstein, A cluster-randomized trial of adjuvanted trivalent influenza vaccine vs. standard in U.S. nursing homes, (Poster presentation, October 5, 2018)(Seqirus-funded researchers found that the adjuvanted vaccine may reduce hospitalization risk of long-stay nursing home residents, compared with standard-dose vaccine, during a predominantly A/H3N2 influenza season, despite reported reduced effectiveness due to egg-based mutagenesis of egg-based vaccines) https://idr.confex.com/idr2018/webprogram/Paper72986.html; S.A. McNeil, et al, Vaccine Effectiveness (VE) of non-adjuvanted and adjuvanted trivalent inactivated influenza vaccines (TIV) in the prevention of influenza-related hospitalization in Canadian seniors over the 2011/12 through 2013/14 season: A pooled analysis from the Serious Outcomes Surveillance (SOS) Network of the Canadian Immunization Research Network (CIRN)(Poster presentation for 12th Canadian Immunization Conference, December 6-8, 2016)(“Our findings demonstrate a trend suggesting increased PE of adjuvanted influenza relative to non-adjuvanted vaccines in an elderly, hospitalized population”).

In 2014, the CDC ACIP made a preferential recommendation for Flumist in healthy children ages 2 to 8, because it seemed to offer better protection.\textsuperscript{16} However, the panel reversed the decision in 2015 because of disappointing performance against the 2009 H1N1 strain.\textsuperscript{17} This reversal has been called a "puzzling development given that scientists in other countries where FluMist is used didn't seem to find the same gap in protection."\textsuperscript{18} Last year, the CDC ACIP voted to include FluMist in the vaccine line-up for the 2018-19 season, returning the vaccine to the U.S. after a two-year hiatus.\textsuperscript{19}

We request that the CDC provide a briefing on these issues to Republican Committee staff. To ensure a productive briefing, CDC should address the following:

1. Could a preferential recommendation increase the percentage of seniors getting vaccinated with any kind of flu vaccine?

2. What other studies or strategies has CDC reviewed on how to increase the vaccination rate of seniors?

3. What kind of effectiveness data has supported past preferential recommendations?

4. What is the precedent for the CDC ACIP to not indicate a preference because the market share of the vaccine that would be subject to the preference is believed to be increasing anyway?

5. What is the basis for CDC's concern about Sanofi's manufacturing capability to support a preferential recommendation for Fluzone HD?

6. What is the basis for CDC's concern that doctors would let senior patients go unvaccinated if the patient requested Fluzone HD that turned out not to be available at the doctor's office?

7. How does the data quality for Fluzone HD and FLUAD compare to that of Flumist, which received a preferential recommendation?

We appreciate your attention to this matter, and if you have any questions, please contact Alan Slobodin of the Republican Committee staff at (202) 225-3641.


\textsuperscript{17} Id.

\textsuperscript{18} Id.

\textsuperscript{19} Id.
Sincerely,

Greg Walden
Republican Leader

Brett Guthrie
Republican Leader
Subcommittee on Oversight
and Investigations

Michael C. Burgess, M.D.
Republican Leader
Subcommittee on Health

cc. The Honorable Frank Pallone, Jr.
cc. The Honorable Diana DeGette
cc. The Honorable Anna Eshoo