Fluzone® High-Dose Vaccine and FIM12 Efficacy Trial Results

Corey A. Robertson, MD, MPH
Director, Scientific and Medical Affairs, Sanofi Pasteur

Older Adults Suffer Disproportionately from Influenza-related Morbidity and Mortality\(^1-3\)

Estimated Annual Number of Hospitalizations Due to Influenza in the US: 226,000

- <65 years of age: 37%
- ≥65 years of age: 63%

Estimated Annual Number of Deaths Due to Influenza in the US: 3,000 to 49,000

- 10%: <65 years of age
- 90%: ≥65 years of age

90% of influenza-related deaths were in people 65 years of age and older

The greatest burden of influenza disease occurs in persons ≥65 years of age despite achieving an immunization rate of 65-70% in this population

## Leading Causes of Hospitalization in Older Adults, United States, 2008-2009

<table>
<thead>
<tr>
<th>Discharge diagnosis</th>
<th>Discharges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease (includes heart attack)</td>
<td>889,000 (392,000)</td>
</tr>
<tr>
<td>Injury</td>
<td>805,000</td>
</tr>
<tr>
<td>Heart failure</td>
<td>758,000</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>652,000</td>
</tr>
<tr>
<td>Stroke</td>
<td>642,000</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>551,000</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>545,000</td>
</tr>
<tr>
<td>COPD*</td>
<td>474,000</td>
</tr>
<tr>
<td>Septicemia</td>
<td>458,000</td>
</tr>
<tr>
<td>Complications of care and adverse effects</td>
<td>405,000</td>
</tr>
</tbody>
</table>

*Note: Data reflect the first listed discharge diagnosis for people 65 years of age and older from nonfederal, short-stay hospitals in the US.

*COPD: Chronic obstructive pulmonary disease.*

Standard-Dose Influenza Vaccine Effectiveness by Age\(^1\)

During the influenza seasons shown, the range of vaccine effectiveness was 62% to 76% in persons 15-64 years of age and 26% to 52% in those ≥65 years of age.


Antibody Responses to Fluzone Influenza Vaccine are Lower in Older vs Younger Adults\(^1\)

\(^a\) GMT: Hemagglutination inhibition geometric mean antibody titer.

Antibody Titers Correlate with Likelihood of Influenza Infection\(^1,2\)

Infection by WRL-105 virus in volunteers previously immunized with monovalent A/Scotland/74 vaccine.

Note: Specific levels of post-vaccination HAI titers have not been correlated with protection. In some studies, titers ≥1:40 have been associated with protection in up to 50% of individuals.

\(^{a}\) HAI: Hemagglutination inhibition antibody


Fluzone High-Dose Vaccine\(^1\)

- Developed by Sanofi Pasteur in response to increasing requests for a vaccine that would improve antibody responses and better protect older adults against influenza
- Formulated to contain 4 times the hemagglutinin (HA) content of Fluzone vaccine
  - 60 mcg HA of each influenza strain per 0.5 mL dose vs. 15 mcg HA/strain
- Fluzone High-Dose vaccine was licensed by the FDA in December 2009 under Accelerated Approval Process
  - Based on superior immunogenicity compared to Fluzone vaccine
- Nearly 15 million doses distributed in the US during the first 3 seasons following licensure and ~8 million doses distributed in 2013-2014
  - More than 1 in 4 immunized persons 65 years of age and older received Fluzone High-Dose vaccine during the 2013-2014 season

FIM12: Post-licensure Efficacy Trial

- Post-licensure commitment study to compare the clinical efficacy of Fluzone High-Dose vaccine and Fluzone vaccine
- Randomized and blinded trial
- ~32,000 participants ≥ 65 years of age enrolled in 126 study sites in the US and Canada
- Trial spanned 2 influenza seasons (2011-2012 and 2012-2013)
- Participants randomized 1:1 to receive 1 dose of Fluzone High-Dose vaccine or Fluzone vaccine and then followed for illness until the end of each season


Primary Analysis: Superior Relative Efficacy Achieved (FIM12)

<table>
<thead>
<tr>
<th></th>
<th>Fluzone High-Dose N=15,892 n (%)</th>
<th>Fluzone N=15,911 n (%)</th>
<th>Relative Efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated with PD ILI</td>
<td>227 (1.43)</td>
<td>300 (1.89)</td>
<td>24.2 (9.7; 36.5)</td>
</tr>
</tbody>
</table>

- Lower limit of the 95% CI of relative efficacy = 9.7%
- Pre-specified lower limit required by FDA to demonstrate superior clinical benefit > 9.1%
- This is the only analysis for which the study was powered

[a] Per-protocol analysis set
[b] Protocol-defined influenza-like illness
Benefit Demonstrated Across Study Years, Influenza Types, and Similarity to Vaccine Strains

Relative Efficacy of Fluzone High-Dose Vaccine vs Fluzone Vaccine

- Year 1 (2011-2012)
- Year 2 (2012-2013)
- Influenza A
- Influenza B
- Similar to Vaccine Strains

Relative Efficacy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Influenza A</th>
<th>Influenza B</th>
<th>Similar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24.2</td>
<td>45.3</td>
<td>20.7</td>
<td>23.6</td>
<td>27.4</td>
</tr>
<tr>
<td></td>
<td>35.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Laboratory-confirmed influenza caused by any viral type or subtype (regardless of similarity) associated with a protocol-defined influenza-like illness.
- Type A and B combined, similar to the vaccine strains by ferret antisera or genomic sequencing data.

Benefit Demonstrated Across Age Groups, Illness Definitions, Methods of Lab Confirmation

Relative Efficacy of Fluzone High-Dose Vaccine vs Fluzone Vaccine

- Age 65–74 yr
- Age ≥ 75 yr
- Illness Definition 2 (Modified CDC-ILI)
- Illness Definition 3 (Respiratory Illness)
- Culture-Confirmed Influenza

Relative Efficacy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Age 65–74 yr</th>
<th>Age ≥ 75 yr</th>
<th>Illness Definition 2</th>
<th>Illness Definition 3</th>
<th>Culture-Confirmed Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24.2</td>
<td>19.7</td>
<td>32.4</td>
<td>20.6</td>
<td>23.1</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

- Laboratory-confirmed (culture and/or PCR) influenza caused by any viral type or subtype (regardless of similarity) associated with a protocol-defined influenza-like illness.
- Full analysis set (subjects categorized as randomized).
- Per-protocol analysis set.
Relative Risk of Pneumonia, Cardio-Respiratory Conditions, and Hospitalizations

- Analyses of the risk of developing specific outcomes following Fluzone High-Dose vaccine relative to Fluzone were also conducted
- Because all ~32,000 participants in FIM12 received either Fluzone or Fluzone High-Dose vaccine, a relatively small proportion of participants experienced laboratory-confirmed influenza
  - Not surprisingly, an even smaller subset suffered pneumonia, cardio-respiratory conditions, or hospitalization
- Nonetheless, FIM12 was large enough to give some indication of the benefits that might be associated with use of Fluzone High Dose vaccine

Relative Risk of Medical Events within 30 days of Illness, Without Regard to Influenza Confirmation
Fluzone High-Dose Vaccine vs Fluzone Vaccine
### Safety Results, Entire Study Period\(^a\) (FIM12)

<table>
<thead>
<tr>
<th>Subjects experiencing at least one:</th>
<th>Fluzone High-Dose (N=15,992)</th>
<th>Fluzone (N=15,991)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>SAE</td>
<td>1323</td>
<td>8.27</td>
</tr>
<tr>
<td>Related SAE</td>
<td>3(^b)</td>
<td>0.02</td>
</tr>
<tr>
<td>AE of Special Interest (AESI)</td>
<td>3(^c)</td>
<td>0.02</td>
</tr>
<tr>
<td>SAE leading to study discontinuation</td>
<td>99</td>
<td>0.62</td>
</tr>
<tr>
<td>Death (any cause)</td>
<td>83</td>
<td>0.52</td>
</tr>
</tbody>
</table>

\(^a\) Full analysis set (subjects categorized by vaccine received)

\(^b\) Related SAEs: Fluzone High-Dose group: left cranial nerve VI palsy (Day 1), hypovolemic shock with diarrhea (Day 1), and acute disseminated encephalomyelitis (ADEM; Day 117)

\(^c\) AESI: Fluzone High-Dose group: Bell’s palsy, ADEM, and Stevens-Johnson Syndrome (Days 53, 117, and 166)

\(^d\) AESI: Fluzone group: 5 cases of Bell’s palsy (Days 9 through 204) and 1 case of Guillain-Barré Syndrome (Day 95)

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### FIM12: Conclusions (1)

- **Fluzone High-Dose vaccine provided superior protection against clinically relevant laboratory-confirmed influenza illness compared to Fluzone vaccine among persons 65 years of age and older**
  - The study results met the FDA-approved pre-specified criteria demonstrating superior efficacy (primary objective)
  - Fluzone High-Dose vaccine reduced all clinically relevant influenza disease, caused by any viral type or sub-type, by a further 24.2% compared to Fluzone vaccine
FIM12: Conclusions (2)

- Secondary objectives were met, demonstrating benefits of Fluzone High-Dose vaccine over Fluzone across:
  - Study years
  - Influenza types
  - Age groups
  - Clinical illness definitions
  - Methods of laboratory confirmation
  - Viral strains, especially those similar to vaccine strains

- Observational analyses demonstrated Fluzone High-Dose compared to Fluzone was associated with fewer cases of:
  - Pneumonia
  - Cardio-respiratory conditions
  - Hospitalizations

- Economic analyses have been conducted; results look encouraging

Fluzone and Fluzone High-Dose Vaccines: Important Safety Information

**Indication**

**Fluzone Vaccine**
Fluzone vaccine is an inactivated influenza virus vaccine indicated for active immunization of persons 6 months of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

**Fluzone High-Dose Vaccine**
Fluzone High-Dose vaccine is an inactivated influenza virus vaccine indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. Approval of Fluzone High-Dose vaccine is based on superior immune response relative to Fluzone vaccine. Data demonstrating a decrease in influenza disease after vaccination with Fluzone High-Dose vaccine relative to Fluzone vaccine have not yet been reviewed by FDA.
Fluzone and Fluzone High-Dose Vaccines: Important Safety Information (2)

Safety Information

Fluzone and Fluzone High-Dose Vaccines

The most common local and systemic adverse reactions to Fluzone and Fluzone High-Dose vaccines include pain, erythema, and swelling at the vaccination site; fever, headache, malaise, and myalgia. Other adverse reactions may occur. Fluzone and Fluzone High-Dose vaccines should not be administered to anyone with a severe allergic reaction (eg, anaphylaxis) to any vaccine component, including egg protein or thimerosal (the multi-dose vial of Fluzone vaccine is the only presentation that contains thimerosal), or to a previous dose of any influenza vaccine.

The decision to give Fluzone or Fluzone High-Dose vaccine should be based on the potential benefits and risks, especially if Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine. Vaccination with Fluzone or Fluzone High-Dose vaccine may not protect all individuals.

Before administering Fluzone and Fluzone High-Dose vaccines, please see full Prescribing Information.

Thank you
**Study Illnesses Definitions (FIM12)**

<table>
<thead>
<tr>
<th>Protocol defined influenza-like illness (PD-ILI)</th>
<th>Modified CDC-defined ILI (Modified CDC-ILI)</th>
<th>Respiratory illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required at least one respiratory symptom and at least one systemic symptom listed below</td>
<td>Required at least one respiratory symptom listed below and fever&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Required at least one respiratory symptom listed below&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Respiratory symptoms:</strong>&lt;br&gt;• Cough&lt;br&gt;• Sore throat&lt;br&gt;• Sputum production&lt;br&gt;• Wheezing&lt;br&gt;• Difficulty breathing</td>
<td><strong>Respiratory symptoms:</strong>&lt;br&gt;• Cough&lt;br&gt;• Sore throat&lt;br&gt;<strong>Systemic symptom:</strong>&lt;br&gt;• Fever &gt; 37.2 °C (&gt; 99.0 °F)</td>
<td><strong>Respiratory symptoms:</strong>&lt;br&gt;• Cough&lt;br&gt;• Sore throat&lt;br&gt;• Sputum production&lt;br&gt;• Wheezing&lt;br&gt;• Difficulty breathing&lt;br&gt;• Sneezing&lt;br&gt;• Stuffy or runny nose</td>
</tr>
<tr>
<td><strong>Systemic symptoms:</strong>&lt;br&gt;• Fever &gt; 37.2 °C (&gt; 99.0 °F)&lt;br&gt;• Chills (shivering)&lt;br&gt;• Tiredness (fatigue)&lt;br&gt;• Headache&lt;br&gt;• Myalgia (muscle ache)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


<sup>b</sup> New onset or exacerbation of a pre-existing condition of at least one respiratory symptom that persisted for or reoccurred after a period of at least 12 hours.
Projected Absolute Efficacy of Fluzone High-Dose Vaccine If 100 Healthy People Are Unvaccinated and Exposed to Influenza…

80 people out of 100 will develop influenza

Unprotected
Relative efficacy
Absolute efficacy

In addition, 24% of the 80 persons who were unprotected by Fluzone vaccine would be protected by Fluzone High-Dose vaccine.

If the absolute efficacy of Fluzone vaccine in a given season is 20%, 20 out of 100 will be protected.

Total number of persons protected by Fluzone High-Dose vaccine = 39

Projected Absolute Efficacy of Fluzone High-Dose Vaccine Based on 24% Relative Efficacy Compared to Fluzone Vaccine