Fluzone® High-Dose Vaccine and FIM12 Efficacy Trial Results

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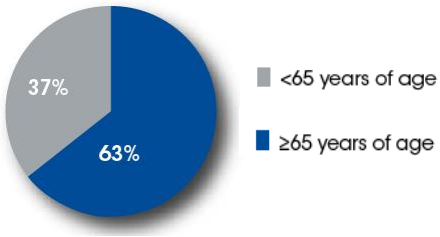
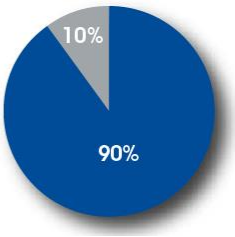
Older Adults Suffer Disproportionately from Influenza-related Morbidity and Mortality[1-3]

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



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



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

References: 1. Centers for Disease Control and Prevention (CDC). *MMWR*. 2009;58(RR-8):1-52. **2.** Poland GA, Mulligan MJ. *J Infect Dis.* 2009;200:161-163. **3.** Thompson WW, et al. *JAMA.* 2004;292(11):1333-1340.

Leading Causes of Hospitalization in Older Adults, United States, 2008-2009[1]

Discharge diagnosis	Discharges
Ischemic heart disease (includes heart attack)	889,000 (392,000)
Injury	805,000
Heart failure	758,000
Pneumonia	652,000
Stroke	642,000
Cardiac arrhythmias	551,000
Osteoarthritis	545,000
COPD[a]	474,000
Septicemia	458,000
Complications of care and adverse effects	405,000

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

[a] COPD: Chronic obstructive pulmonary disease.

Reference: 1. National Center for Health Statistics. *Health—United States, 2011*. Table 104, pp 335-336. http://www.cdc.gov/nchs/data/hus/hus11.pdf. Accessed January 31, 2013.

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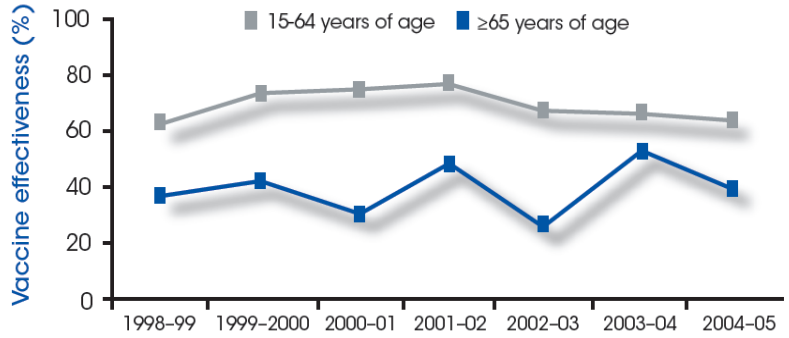
Standard-Dose Influenza Vaccine Effectiveness by Age[1]



Adapted from Monto, 2009.

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

Reference: 1. Monto AS, Ansaldi F, Aspinall R, et al. Influenza control in the 21st century: optimizing protection of older adults. *Vaccine.* 2009;27:5043-5053.

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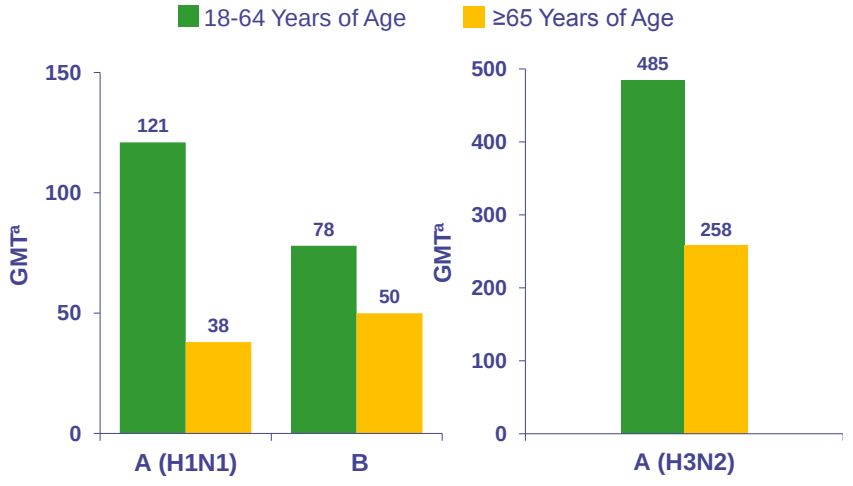
Antibody Responses to Fluzone Influenza Vaccine are Lower in Older vs Younger Adults[1]



[a] GMT: Hemagglutination inhibition geometric mean antibody titer.

Reference: 1. Sanofi Pasteur Inc. Data on file (Annual study GRC41), November 2009. MKT20203.

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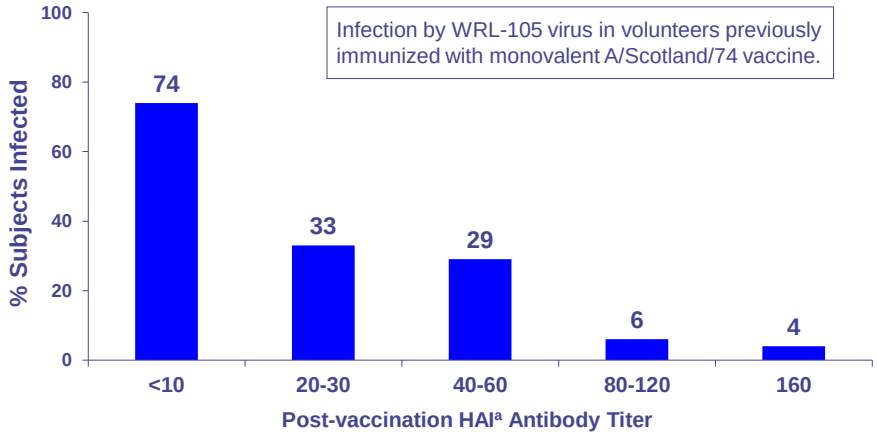
Antibody Titers Correlate with Likelihood of Influenza Infection[1,2]



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

References: 1. Potter CW, Oxford JS. *Br Med Bull.* 1979;35(1):69-75. **2.** Hannoun C, et al. *Virus Res.* 2004;103(1-2):133-138.

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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**

Reference: 1. Fluzone High-Dose vaccine [Prescribing Information]. Swiftwater, PA: Sanofi Pasteur Inc.; 2013.

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FIM12: Post-licensure Efficacy Trial[1]

- 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

Reference: 1. Clinicaltrials.gov. A study of Fluzone High-Dose vaccine compared with Fluzone vaccine in elderly adults. http://www.clinicaltrials.gov/ct2/show/NCT01427309.

Primary Analysis: Superior Relative Efficacy Achieved (FIM12)

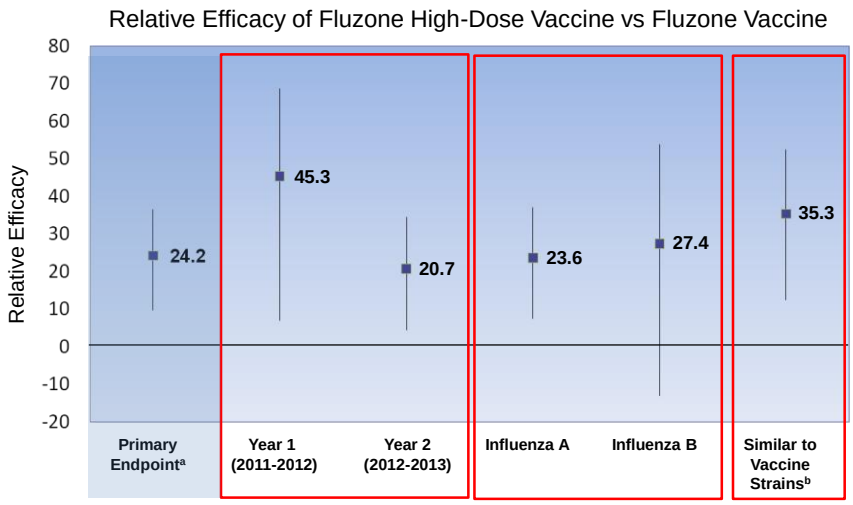
Laboratory-confirmed influenza caused by any viral type or subtype (regardless of similarity)[a]

	Fluzone High-Dose N=15,892 n (%)	Fluzone N=15,911 n (%)	Relative Efficacy % (95% CI)
Associated with PD ILI[b]	**227 (1.43)**	**300 (1.89)**	**24.2 (9.7; 36.5)**

- **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



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

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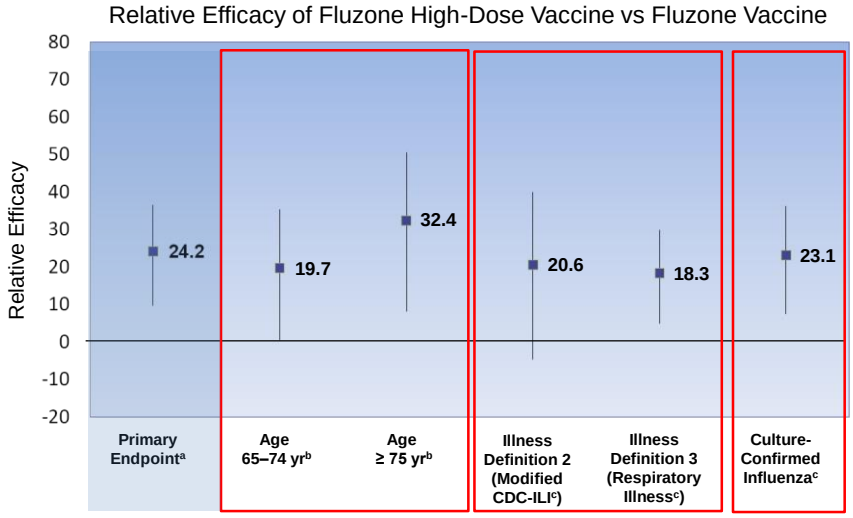
Benefit Demonstrated Across Age Groups, Illness Definitions, Methods of Lab Confirmation



[a] 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.
[b] Full analysis set (subjects categorized as randomized).
[c] Per-protocol analysis set.

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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

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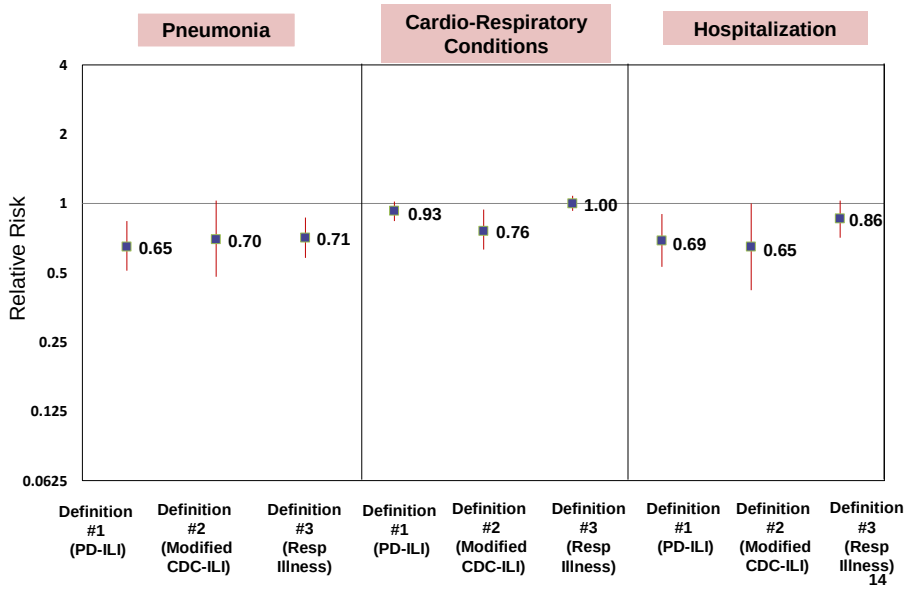
Relative Risk of Medical Events within 30 days of Illness, Without Regard to Influenza Confirmation Fluzone High-Dose Vaccine vs Fluzone Vaccine



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Safety Results, Entire Study Period[a] (FIM12)

	Fluzone High-Dose (N=15,992)		Fluzone (N=15,991)	
Subjects experiencing at least one:	**n**	**%**	**n**	**%**
SAE	1323	8.27	1442	9.02
Related SAE	3[b]	0.02	0	0.00
AE of Special Interest (AESI)	3[c]	0.02	6[d]	0.04
SAE leading to study discontinuation	99	0.62	103	0.64
Death (any cause)	83	0.52	84	0.53

[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

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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

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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.

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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.

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Thank you

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Back-up Slides

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Study Illnesses Definitions (FIM12)

Protocol defined influenza-like illness (PD-ILI)	Modified CDC-defined ILI (Modified CDC-ILI)	Respiratory illness
Required at least one respiratory symptom and at least one systemic symptom listed below	Required at least one respiratory symptom listed below and fever[a]	Required at least one respiratory symptom listed below[b]
Respiratory symptoms: • Cough • Sore throat • Sputum production • Wheezing • Difficulty breathing **Systemic symptoms**: • Fever > 37.2 °C (> 99.0 °F) • Chills (shivering) • Tiredness (fatigue) • Headache • Myalgia (muscle ache)	**Respiratory symptoms**: • Cough • Sore throat **Systemic symptom**: • Fever > 37.2 °C (> 99.0 °F)	**Respiratory symptoms**: • Cough • Sore throat • Sputum production • Wheezing • Difficulty breathing • Sneezing • Stuffy or runny nose

[a] The CDC defines fever as a temperature of 37.8°C (>100.0°F), available at: http://www.cdc.gov/vaccines/pubs/surv-manual/chpt06-influenza.pdf (accessed Jan 11, 2014).

[b] 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.

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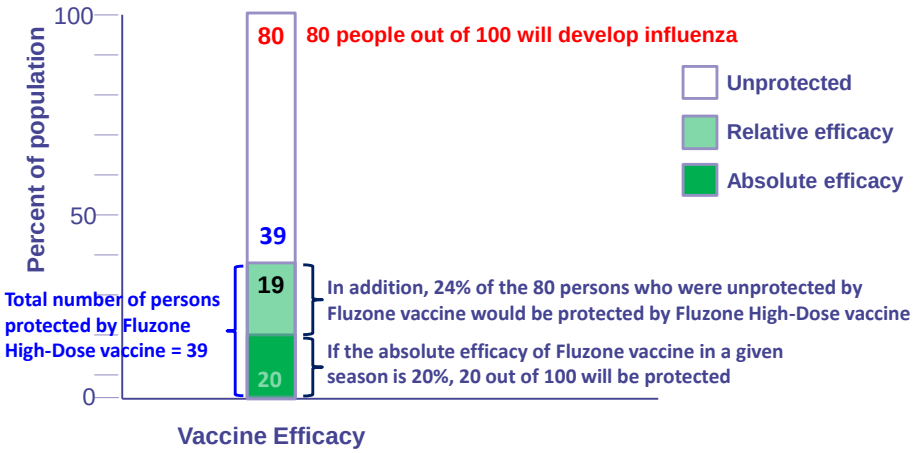
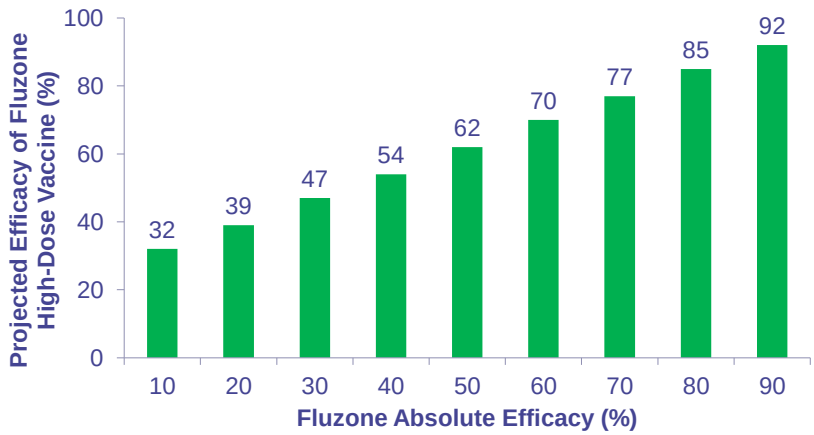
Projected Absolute Efficacy of Fluzone High-Dose Vaccine If 100 Healthy People Are Unvaccinated and Exposed to Influenza…



References: **1.** Monto AS, et al. *NEJM* 2009;361(13):1260-7. **2.** Ohmit SE, et al. *J Infect Dis* 2008;198(3):312-7. **3.** Ohmit SE, et al. *NEJM* 2006;355(24):2513-22. **4.** Belshe RB, et al. *NEJM* 2007;356(7):685-96. **5.** Vesikari T, et al. *NEJM*. 2011;365(15):1406-16. **6.** Wang Z, et al. *JAMA* 2009;301(9):945-53. **7.** CDC. Principles of Epidemiology in Public Health Practice, 3rd Edition, available at: http://www.cdc.gov/osels/scientific_edu/SS1978/Lesson3/Section6.html (accessed Jan 6, 2014).

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



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