

# Call to Action

## Reinvigorating Influenza Prevention in US Adults Age 65 Years and Older



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#### Protecting the 65+ Population against Influenza

In the US, adults age 65 years and older are disproportionately impacted by influenza (flu) every year.<sup>1-4</sup> There are far more flu-related deaths and hospitalizations in adults age 65 years and older than any other age group. Months after recovering from flu symptoms, older adults may still be at an increased risk of a heart attack, stroke, or other cardiovascular problems.<sup>5</sup> The increased risk is due to lingering inflammation and increased risk of blood clots that may be associated with infections like influenza. Additionally, even when all of these risks have passed, older adults may be left facing the reality that they will never fully regain their pre-influenza health and abilities, significantly impacting their lifestyle.<sup>6</sup>

Both the increased likelihood of chronic conditions with age and the gradual deterioration of the immune system due to aging (immunosenesence) result in an elevated risk of complications from flu and other infections in adults age 65 years and older.<sup>7</sup> Immunosenesence is also a factor in reduced vaccine efficacy in older adults. But age alone does not predict the severity of

immunosenesence. Frailty, manifested as unintentional weight loss, self-reported exhaustion, weak grip strength, slow walking speed, and low physical activity<sup>8</sup> may more accurately predict the degree of immunosenesence and lowered response to vaccination than age alone.<sup>9,10</sup>

Despite the well-publicized risks that flu poses for older adults, US influenza vaccination coverage has stalled in adults age 65 years and older over the last few seasons, and unfortunately dropped from 66.8 percent in the 2014-2015 season down to 63.4 percent in the 2015-2016 season.<sup>11</sup> Influenza vaccine coverage rates are actually higher in infants age six to 23 months (75 percent) and toddlers/preschoolers age two to four years (69 percent), which is particularly notable since vaccination has been recommended for adults age 65 years and older since 1973 and for children only since 2004. There are many well-documented barriers to influenza vaccination,<sup>12-16</sup> but one—the perception that influenza vaccination is not effective in older adults—may be answered (at least in part) by vaccines approved specifically for those age 65 years and older. While influenza vaccines cannot prevent every case of flu in older adults, vaccination reduces the risk of

hospitalization, death, and long-term physical decline that older adults may experience with influenza.<sup>17</sup>

The National Foundation for Infectious Diseases (NFID) convened a roundtable to examine the impact of flu in the 65+ population. Public health and medical experts, along with health and consumer advocates examined the impact of flu in adults age 65 years and older, discussed ways to improve vaccination rates in this vulnerable population, and considered the role of vaccines designed to provide better protection from the serious complications of flu in older adults.

## Flu in Older Adults and the Increased Risk of Heart Attack and Stroke

Flu in older adults can have a somewhat different clinical presentation than what many think of as traditional flu symptoms. The sudden onset of high fever typical in children and younger adults may be replaced by malaise in older adults.<sup>18,19</sup> Sore throat, runny nose, and nasal congestion are all less frequent in older adults, while gastrointestinal symptoms (e.g., pain, diarrhea, nausea, or vomiting) are more frequent.

Bacterial lung infection (bronchitis or pneumonia) is the most common complication of flu, but flu can have additional complications. Flu and pneumonia can raise the risk of a first or subsequent heart attack by three to five times in the first weeks after infection and the risk remains elevated for several months (Table 1).<sup>5</sup> Similarly, the risk of a first or subsequent stroke is increased two to three times in the first two weeks after infection and remains somewhat elevated for several months. The risk of heart attack and stroke remains elevated by about one-third for as long as three months after influenza infection.<sup>5</sup>

While influenza infection is positively correlated with the risk of heart attack and stroke, one study reported a negative correlation between influenza vaccination and the rate of first heart attack or stroke (Table 1).<sup>5</sup> When compared with unvaccinated individuals, those vaccinated had a lower risk of these outcomes in the months following vaccination.

Older adults may experience both fewer systemic symptoms and localized respiratory symptoms based on their immune system response.<sup>18,19</sup> Influenza infection can trigger a systemic inflammatory response that increases more slowly and lasts much longer in older adults compared to younger adults (often up to a week).<sup>20</sup> While short-term (acute) inflammation is a way for the body to fight infection and produces a prothrombotic state associated with vascular events, long-term (chronic) inflammation increases the risk of heart disease, cancer, and other serious illnesses.<sup>21</sup>

Finally, influenza infection is often associated with a significant negative impact on an older adult's ability to function independently. A study that included nearly 250,000 US nursing home residents showed a strong correlation between the severity of the circulating influenza strains and the decrease residents experienced in their ability to perform daily tasks such as dressing themselves, bathing, going to the bathroom alone, and eating meals without assistance.<sup>6</sup> The level of functional decline measured in the study can be reversed in less than 10 percent of long-term care residents, suggesting that the impact of flu is likely permanent.

**Table 1: Age-Adjusted Incidence Ratio of First Myocardial Infarction and First Stroke After Influenza Vaccination or Infection<sup>5</sup>**

Risk Period (days)	Myocardial Infarction				Stroke			
	Influenza Vaccination (N = 20,486)		Systemic Respiratory Infection (N = 20,921)		Influenza Vaccination (N = 19,063)		Systemic Respiratory Infection (N = 22,400)	
	Cases, n	IR (95% CI)	Cases, n	IR (95% CI)	Cases, n	IR (95% CI)	Cases, n	IR (95% CI)
1-3	77	0.75 (0.60-0.94)	322	4.95 (4.43-5.53)	76	0.77 (0.61-0.96)	244	3.19 (2.81-3.62)
4-7	94	0.68 (0.56-0.84)	276	3.20 (2.84-3.60)	95	0.72 (0.59-0.88)	237	2.34 (2.05-2.66)
8-14	176	0.73 (0.63-0.85)	422	2.81 (2.54-3.09)	194	0.84 (0.73-0.96)	368	2.09 (1.89-2.32)
15-28	417	0.87 (0.79-0.96)	576	1.95 (1.79-2.12)	409	0.88 (0.80-0.97)	561	1.68 (1.54-1.82)
29-91	2,154	1.03 (0.98-1.08)	1,658	1.40 (1.33-1.48)	2,051	1.01 (0.96-1.06)	1,650	1.33 (1.26-1.40)
Baseline period	17,533	1.00 –	17,099	1.00 –	16,188	1.00 –	18,056	1.00 –

Abbreviations: CI = confidence interval; IR = incidence ratio.

## Hospitalizations and Deaths from Influenza Increase with Age

The severity of influenza circulating in the community changes from year-to-year, but it is consistent that adults age 65 years and older disproportionately suffer from the most serious outcomes.<sup>1-4</sup> Annual variation in flu severity affects the cumulative rates of laboratory-confirmed influenza hospitalizations in adults age 65 years and older (Figure 1), but a consistent and sharp increase in hospitalizations typically begins just before the end of the year, and continues for about six to eight weeks before leveling off.<sup>2</sup> In the severe 2014-2015 flu season, there were more than 300 hospitalizations in the US for every 100,000 adults age 65 years and older.

While there are far more flu cases in younger adults, those age 65 years and older account for the majority of hospitalizations (Figure 2).<sup>1</sup> In the 2014-2015 season, in which a drifted H3N2 strain predominated and reduced vaccine effectiveness,

757,823 of the estimated 974,206 hospitalizations (78 percent) were in adults age 65 years and older.<sup>22</sup>

US surveillance systems do not track annual flu-related deaths directly, except among children, but statistical methods estimate an influenza-related all-cause death rate of 133 per 100,000 in adults age 65 years and older, more than six times the rate of 20 per 100,000 across all ages.<sup>4</sup> These findings are consistent with estimates from other countries, where the mortality rates are seven to 11 times higher in those age 65 years and older than the general population.<sup>23-25</sup>

## The Burden of Flu in the Aging Population

The first influenza virus subtype a person is exposed to may determine how they respond to different viruses later in life.<sup>26</sup> Adults currently aged 65 years and older were most likely first exposed to influenza A (H1N1), which was the

predominant circulating influenza strain until 1947. In seasons where this strain predominates today, adults age 65 years and older experience lower rates of hospitalization and death compared to seasons when influenza A (H3N2) is the more common virus.

Today's baby boomers, born between 1946 and 1964, may have less protection from influenza A (H1N1). Since it did not circulate as widely when they were young, they are less likely to have had their initial influenza exposure to this virus group. As baby boomers age into the 65+ population, they may be more susceptible to influenza A (H1N1) strains. This may result in a higher burden of disease as this generational group ages.

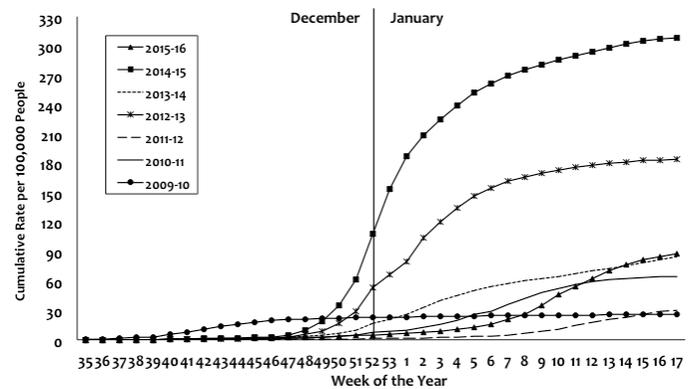
## Improving Influenza Vaccines for Older Adults

A variety of strategies have been considered for developing influenza vaccines that are able to overcome age-related immunosenescence.<sup>27</sup> Two vaccines have received US Food and Drug Administration (FDA) approval for use in the US in adults age 65 years and older.

Fluad™, an adjuvanted influenza vaccine for adults age 65 years and older, was first approved for use in the US for the 2016-2017 season. The vaccine has been in use in Italy since the 1990s and is licensed for use in 38 other countries including Canada and 15 countries in Europe.<sup>28</sup> Vaccine safety has been confirmed in clinical and observational studies including approximately 120,000 subjects; and by 2013 more than 60 million doses had been distributed for use in older adults worldwide.<sup>29</sup> The vaccine is associated with more injection site reactions compared to standard-dose vaccine.

In a randomized, observer-blinded, multicenter clinical trial of 7,104 adults age 65 years and older

**Figure 1: Cumulative Hospitalization Rates\* in Adults Age ≥65 Years<sup>2</sup>**

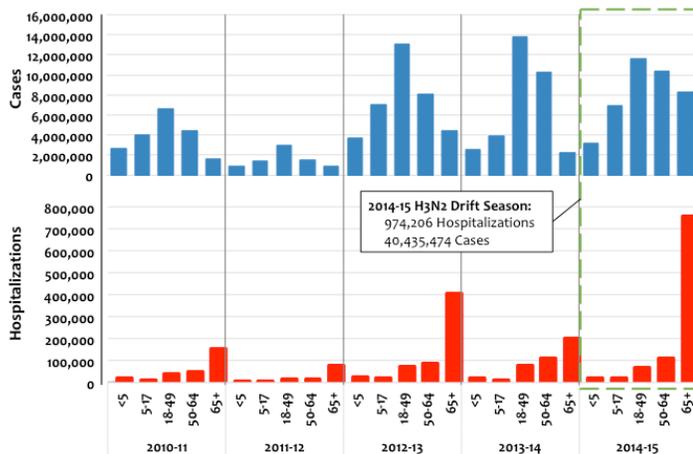


\*Cumulative rate per 100,000 for laboratory-confirmed influenza hospitalizations in the US

(mean age, 72 years), adjuvanted influenza vaccine elicited a higher antibody response than standard-dose vaccine for all three influenza strains (A/H1N1, A/H3N2, and B), and for both homologous and heterologous A strains.<sup>30</sup> However, pre-established superiority criteria by the FDA were met only for influenza A (H3N2), the strain causing the most severe disease across all age groups.

There are no prospective, randomized efficacy trials reported, but a number of observational studies have reported on the effectiveness of adjuvanted influenza vaccine in older adults. In a large cohort study (170,988 person-seasons of observation) conducted in Italy over three seasons, the risk of hospitalization from influenza or pneumonia was 25 percent lower in patients who received adjuvanted vaccine compared with standard vaccine.<sup>31</sup> In a Canadian case control study (N=282), adjuvanted vaccine was superior to standard vaccine in preventing influenza infection in nursing home patients.<sup>32</sup> An Italian prospective cohort study of 3,173 nursing home residents with a mean age of 85 years reported protection rates of 80 percent for adjuvanted vaccine versus 57 percent for standard-dose vaccine.<sup>33</sup>

**Figure 2: Influenza Hospitalization Rates Highest in Adults Age ≥65 Years in the US<sup>1,22</sup>**



Fluzone® High-Dose, which contains four times more antigen than standard-dose vaccine (60 mcg hemagglutinin of each influenza strain per 0.5 mL dose versus 15 mcg for standard dose), was licensed in the US in 2009 and has been approved for use in those age 65 years and older since the 2010-2011 season. Since introduction, more than 50 million doses have been distributed in the US, and during the 2015-2016 season, approximately 50 percent of US seniors who received any influenza vaccine received high-dose vaccine.<sup>34</sup> Vaccine safety has been established in pre- and many post-licensure studies as well as in clinical use. The vaccine is associated with more injection site reactions compared to standard-dose vaccine.

In a randomized, double-blind, multicenter clinical trial of 3,876 adults age 65 years and older (mean age 73 years), high-dose vaccine elicited significantly higher antibody responses compared with standard-dose vaccine for all three influenza strains (A/H1N1, A/H3N3, and B).<sup>35</sup> The high-dose vaccine met superiority criteria for both A strains.

Since the introduction of the high-dose vaccine, five publications have reported on a

post-licensure efficacy trial.<sup>36-40</sup> A two-season randomized, double-blind trial of nearly 32,000 adults age 65 years and older reported that recipients of the high-dose vaccine had a 24.2 percent lower risk of symptomatic laboratory-confirmed influenza compared to recipients of standard-dose vaccine and the high-dose vaccine met pre-specified FDA superiority criteria.<sup>36</sup> This trial also showed that high-dose vaccine was associated with a 7 percent relative reduction in all-cause hospitalizations, an 18 percent relative reduction in cardiorespiratory events potentially related to flu, and a 40 percent relative reduction in pneumonia.<sup>38</sup>

An economic analysis using outcome data from the randomized controlled efficacy trial reported a saving of \$116 in direct healthcare payer costs per high-dose vaccine recipient compared to standard-dose vaccine recipients.<sup>39</sup> A retrospective cohort study conducted by investigators at FDA, Centers for Disease Control and Prevention (CDC), and Centers for Medicare and Medicaid Services (CMS) of 929,730 high-dose vaccine recipients and 1,615,545 standard-dose vaccine recipients reported that high-dose vaccine was 22 percent more effective in preventing probable influenza infection and 22 percent more effective in preventing flu-related hospitalizations and emergency department visits compared to standard-dose vaccine.<sup>41</sup>

## Influenza Vaccine Options for the 65+ Population

CDC recommends annual influenza vaccination for all eligible individuals age six months and older, optimally before the onset of flu activity in the community, but vaccination should continue for as long as influenza continues to circulate.<sup>42</sup> In the US, adults age 65 years and older currently have multiple vaccine options available, including high-dose

and adjuvanted vaccines, in addition to standard-dose three- and four-strain vaccines (trivalent and quadrivalent vaccines).

Influenza vaccine effectiveness varies seasonally based on the match between circulating and vaccine strains and the specific measures of effectiveness that are studied.<sup>43</sup> Vaccine effectiveness measures may range from prevention of influenza infection to prevention of death, with many outcome measures in between—each of which will result in a unique estimate of effectiveness. Regardless of the measure studied, effectiveness of the standard-dose vaccine tends to decrease with increasing age. However, CDC and the medical community agree that vaccination with any available influenza vaccine, including standard-dose, is better than not vaccinating at all, regardless of the patient's age.

## Challenges to Protecting the 65+ Population Against Influenza

Certain barriers to influenza vaccination may be more relevant for adults age 65 years and older compared to younger adults. Older adults are more likely to have chronic diseases and as these patients worry about managing their underlying medical conditions, they may overlook an annual influenza vaccine. Although primary care healthcare professionals (HCPs) are more likely to vaccinate in their offices, patients with chronic diseases may see specialists more often than primary care HCPs. For this reason, it is imperative that all HCPs, specialists and non-specialists alike, make a strong influenza vaccine recommendation to every patient during flu season to minimize missed opportunities.

While the universal recommendation for all adults to receive an annual influenza vaccination appears simple, there are several vaccines approved for the 65+ population. Older adults may be confused about which vaccine to get or they may have a preference for a vaccine that is not available in all locations. In all cases, vaccination should be the primary goal—older adults may receive the high-dose or adjuvanted vaccine if it is available but should not forego vaccination in any case.

Finally, there may be cost considerations. Medicare provides full coverage for influenza vaccines, regardless of which influenza vaccine a patient receives. For HCPs, however, the cost to purchase different types of vaccine may vary and may influence how much and which vaccine(s) they stock. This may make it difficult, particularly for large systems, nursing homes, and community immunizers to stock every type of vaccine and provide optimal protection for older adults.

## Best Practices for Flu Prevention in the 65+ Population

In the US, approximately one-third of adults age 65 years and older forego annual influenza vaccination, illustrating the ongoing need for education and awareness among the public and HCPs who care for this population. Improving influenza vaccination coverage requires ongoing annual collaborative efforts among public health officials, advocacy groups, professional societies, and other vaccine stakeholders including HCPs and the public. All stakeholders should support and encourage efforts to include influenza vaccination in quality and performance measures, both on the local and national levels. A summary of key best practices to increase influenza vaccination rates in the 65+ population follows (page 7).

## Best Practices to Increase Influenza Vaccination Rates

### Be prepared to answer patient questions (whether or not vaccines are provided)

While influenza vaccination recommendations may appear simple (annual vaccination for all), questions persist among HCPs, patients, families, and health system administrators. HCPs should be knowledgeable about influenza vaccine options and armed with simple and quick answers to frequently asked questions (see page 10). It is important for both primary care HCPs and specialists to understand the benefits of influenza vaccines licensed in the US specifically for adults age 65 years and older. A strong HCP recommendation is important, even in practices that do not offer vaccines, because it is significantly associated with increased vaccination uptake.<sup>12,15,44</sup>

### Walk the walk and ensure all staff are vaccinated annually against influenza (and up-to-date on other recommended vaccines)

HCPs must set a good example and protect patients by getting vaccinated and making sure everyone who cares for or comes in contact with patients has been vaccinated. Additionally, practices with a vaccinated staff are less likely to suffer from absenteeism or presenteeism (employees coming to work sick and performing sub-optimally during winter respiratory season when patients most need them). Leaders need to make their vaccine commitment known to every staff member, both clinical and administrative, and ensure that all staff echo this commitment. Recent findings from CDC on vaccination coverage among HCPs indicate that the 2015-2016 season showed the highest numbers vaccinated to date, even among those in ambulatory care.<sup>45</sup> This clearly supports important messaging to the public: “Your healthcare professional got vaccinated, shouldn’t you?”

### Plan ahead for flu season

It is often hard to plan ahead when there are so many competing demands on HCPs, but time spent planning before flu season can result in a healthier patient base and reduced demand for healthcare services during the winter respiratory virus season. It is important to start this preparation with staff early; team buy-in is essential to success. The most effective and successful models for increasing vaccination rates focus on frequent and consistent positive vaccine messages by all staff. Standing orders improve vaccination coverage and should be considered in all practice environments.<sup>46</sup>

### Address influenza vaccination coverage gaps in African-American and Hispanic patients

While it is important to increase influenza vaccination coverage in the entire 65+ population, there are larger coverage gaps in African-American and Hispanic adults age 65 years and older compared to the overall population. Standardized offering of influenza vaccine has been shown to decrease disparities in vaccination coverage between white and non-white patient populations. Targeted efforts should focus on identifying and addressing specific concerns or knowledge gaps that limit influenza vaccine uptake in these populations.

### Partner with and utilize community resources

Check with your local public health department to see what vaccination services they offer and what information they can provide to help prepare for flu season. While it would be optimal for every US healthcare practice to provide every type of influenza vaccine, this is often not the case. Many pharmacies—both independent and national chains—differ in the influenza vaccine options they have available throughout the season. Influenza vaccines may also be available at senior and community centers, local public health clinics, and many retail stores. Up-to-date information on vaccine availability in local areas is available online at [vaccine.healthmap.org](http://vaccine.healthmap.org).

## Summary

There are now more vaccine options available in the US than ever before, including high-dose and adjuvanted influenza vaccines approved specifically for adults age 65 years and older, and in recent years, vaccine supply has met or exceeded demand. Medicare pays for influenza vaccines in full. Influenza vaccines are available in more locations than ever before, including the traditional doctor's office, public and community health clinics, pharmacies, and workplaces.

Public health officials, medical professionals, professional societies, and others who are part of the US vaccine infrastructure must take advantage of every opportunity to provide optimal protection for adults age 65 years and older and continue to work collaboratively to remove any ongoing barriers to vaccination.

## Participating Organizations

Representatives from the following organizations participated in the July 2016 NFID Roundtable, which served as the basis for this report.

- AARP
- Alliance for Aging Research
- American Academy of Family Physicians
- American College of Physicians
- American Lung Association
- Centers for Disease Control and Prevention
- Gerontological Society of America
- Griffith University School of Medicine (Australia)
- Immunization Action Coalition
- National Foundation for Infectious Diseases
- University of Arkansas for Medical Sciences College of Medicine
- University of Maryland School of Medicine
- University of Michigan
- Vanderbilt University School of Medicine

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# Frequently Asked Questions about Influenza Vaccination for Adults Age 65 Years and Older

## When should I get a flu vaccine?

You should get an annual influenza vaccine as soon as it is available in your area. However, as long as flu viruses are circulating, vaccination should continue throughout the flu season, even in January or later.

## Which flu vaccine is best for me?

If you are age 65 years or older, you may want to consider one of the flu vaccines specially approved for the 65+ population, but getting any influenza vaccine is better than not getting vaccinated at all.

## Does the flu vaccine work?

Yes, influenza vaccines work! How well they work can vary each year because different influenza viruses circulate each year. Also, vaccines may not prevent infection completely as we age, but getting vaccinated can make the flu less severe if you do get it and also lower your risk of hospitalization, heart attack, and death, among other serious complications.

## I want the special vaccine for adults age 65 years and older, but I'm having trouble finding it. What should I do?

You can check [vaccine.healthmap.org](http://vaccine.healthmap.org) to see which vaccines are available in your area, or you can call local pharmacies or senior centers. But do not delay in getting whichever vaccine is available—it takes about two weeks for the influenza vaccine to become effective once administered. A vaccination deferred is often a vaccine not received.

## I'm allergic to eggs. Can I still get a flu vaccine?

If you only get hives after exposure to eggs then you can get any influenza vaccine. If you have had a more serious reaction, such as swollen lips and lightheadedness, or have trouble breathing and need emergency medical care, you should still get vaccinated, but either in a location where a healthcare professional can monitor you for an allergic reaction after you have been vaccinated or with a special vaccine that is made with no egg allergens.

## I've never had the flu so why do I need to get a vaccine?

There is no way to tell who will get the flu each year or how severe the illness will be. Even if you feel perfectly healthy, you are at higher risk of serious outcomes from the flu as you get older, including being hospitalized or having a heart attack or a stroke.

## Can't the vaccine give me the flu?

The influenza vaccine cannot give you the flu. People sometimes get sick shortly after they get vaccinated and they assume there is a connection. This is not from an influenza infection, but could be just part of how they feel as their body develops immunity. Also, during the fall and winter respiratory virus seasons, people tend to get sick more often. There is a chance that it happens close to when you got vaccinated, but that does not mean it was caused by vaccination.

## What is the difference between influenza vaccines specifically approved for adults 65+ and standard influenza vaccines?

As people age, their immune system may not respond as well, decreasing the body's ability to respond to vaccination. Influenza vaccines for those 65+ are designed to help improve the response of your immune system to vaccination and increase your chances of being protected against the flu.

## How do I know that the vaccines are safe?

Like all vaccines approved by the US Food and Drug Administration (FDA), all influenza vaccines have undergone extensive testing and research.

For additional information, visit [www.nfid.org/flu](http://www.nfid.org/flu)

