Influenza in Older Adults

H. Keipp Talbot, MD, MPH

KEYWORDS
- Influenza
- Vaccine
- Aging
- Antivirals

KEY POINTS
- Influenza viruses circulate yearly and cause significant disease in the elderly.
- Influenza often presents atypically in older adults.
- New influenza vaccines are being developed for older adults to overcome immune senescence.

INTRODUCTION

Influenza viruses cause significant morbidity and mortality in older adults. Prevention and treatment are critical for the reduction of morbidity and mortality in this population, but there are several challenges in the diagnosis, treatment, and prevention of influenza infection and its complications in older adults. This article will describe influenza, its epidemiology, clinical presentation, diagnostic modalities, treatment, and current prevention techniques. Despite the identification of influenza early in the last century, much is still not known about how to protect older adults from influenza infection and its complications. Current treatment and prevention strategies are imperfect, particularly in older frail adults.

VIROLOGY

Influenza is a segmented RNA virus of the orthomyxoviridae family that circulates annually. Influenza A and B are both known to cause disease in people. Because the virus is a segmented RNA virus, it has the capability of making minor (called antigenic drift) or major (called antigenic shift) changes to its genome, causing seasonal or pandemic outbreaks of disease, respectively. Influenza A subtypes are differentiated by the type of hemagglutinin and neuraminidase found on their outer surface (eg, H1N1 and H3N2 subtypes). The hemagglutinin protein is responsible for viral receptor binding and fusion with the host respiratory epithelial cell. This surface protein undergoes frequent genetic mutations that allow for the circulating strain to potentially escape recognition by the host’s immune system. The neuraminidase, also a glycoprotein, facilitates the release of daughter virions from infected cells. For unknown
reasons, seasonal influenza A/H3N2 viruses are associated with higher morbidity and mortality than either seasonal influenza A/H1N1 or influenza B viruses. There are 2 main lineages of influenza B that circulate in the human population, B/Yamagata and B/Victoria. Traditionally 1 of the B lineages has been chosen for inclusion into the yearly vaccine, but most vaccine manufacturers are now including a virus from both B lineages due to poor predictability of the circulating lineage in the coming year. Multiple influenza viruses can circulate in a season (usually December through March), and a patient can be infected by more than 1 virus in a season.

**EPIDEMIOLOGY OF INFLUENZA**

Because the circulating influenza virus often changes from year to year, the morbidity and the mortality from influenza also fluctuate. In any given year, influenza accounts for 2% to 20% of cardiopulmonary hospitalizations. Estimates of hospitalization and death in the United States due to influenza infection range from 1.287 to 2.127 million hospitalizations and 961 to 14,715 deaths, respectively. Many of the deaths are secondary to pneumonia or cardiac complications and are much more common in the older than in the younger populations. Once infected, 67% of elderly become at least temporarily housebound, and 25% become temporarily bedbound. Despite prior exposure to many influenza viruses in the past, the incidence of this morbidity and mortality continues to increase with age likely because of immune senescence and higher number of comorbid conditions present in older adults.

Influenza viruses are among the leading causes of outbreaks in long-term care facilities, with attack rates that span 4% to 94% of residents (mean 33%). Mortality rates in these outbreaks may approach 55%.

**CLINICAL PRESENTATION**

The classic, textbook presentation of influenza is fever, cough, and general aches (often called an influenza-like illness or ILI) lasting 3 to 7 days. The presentation of older adults with influenza is neither classic, nor simple. Fever may not be prominent even when fever is defined as temperature greater than 99°F, and the presenting complaints may instead consist of exacerbations of underlying health problems like congestive heart failure or chronic obstructive pulmonary disease (COPD).

In one study of veterans with COPD 50 years of age and older, the prominent presentation of influenza was cough, sputum production, and dyspnea. Only 64% of laboratory-confirmed cases of influenza were associated with either documented or subjective fever. In a cohort of vaccinated adults 60 years of age and older, fever was even less common, with only 39% of patients with laboratory-confirmed influenza complaining of fever, while 94% reported coryza. The lack of fever in this cohort, however, could have been due to vaccination of everyone in the cohort.

In the inpatient setting, the most common presentation of influenza is cough (96%), with only 64% of patients reporting being febrile. One hospital-based surveillance study found that only 51% of hospitalized adults with influenza had the classic ILI presentation. Because of this atypical presentation, influenza is often not associated with the reason for hospitalization by many providers. Providers should have a low threshold for testing and treating older adults.

**DIAGNOSIS**

The diagnosis of influenza is not only important to epidemiologists but also to individual clinicians who care for older individuals. The laboratory method that has been
available for clinical use the longest has been culture isolation of influenza, which requires several days until definitive results are available. With recommendations to start antiviral treatment within 48 hours of symptom onset, the delay in culture results makes it less than ideal for rapid therapeutic intervention. Rapid antigen testing is a popular modality to obtain an influenza diagnosis quickly. This works well in children who secrete large amounts of virus. Adults, however, shed much less virus than children and tend to shed for shorter periods of time, thus reducing the utility of rapid antigen tests in this population. A study in hospitalized patients found the sensitivity of the rapid antigen test performed at bedside was only 19% (95% confidence interval [CI], 8.51%–37.9%); and the sensitivity of conventional influenza culture was 34.6% (95% CI, 19.4%–53.8%).

Recently, polymerase chain reaction (PCR), a common diagnostic tool in research settings, has been shown to be more sensitive than culture for the detection of influenza. With the introduction of PCR into clinical laboratories, the sensitivity of influenza diagnosis has improved. The sensitivity of PCR in adults 40 years of age and older is greater than 90%. Unfortunately, not all clinical laboratories perform PCR at all, or if they do, some may not perform this test daily. When possible, PCR should be used for diagnosis, as it is the most sensitive method. If PCR not available, results of antigen testing should be remembered to have poor sensitivity.

TREATMENT

Currently 2 classes of antiviral medications active against influenza, the adamantanines and neuraminidase inhibitors, are licensed in the United States. Because of the development of resistance to adamantanines, these agents are no longer used clinically. Neuraminidase inhibitors are currently the only recommended pharmacologic treatment for influenza. They work by blocking the neuraminidase glycoprotein noted earlier. Three neuraminidase inhibitors are currently available in the United States: peramivir, oseltamivir, and zanamivir. Peramivir is the most recently licensed neuraminidase inhibitor and is given intravenously; oseltamivir is given orally, and zanamivir is delivered by inhalation. Both peramivir and oseltamivir need to be dosed based on renal function. Zanamivir should be used cautiously in adults with reactive airway disease, as some patients have developed bronchospasm. Early studies of neuraminidase inhibitors noted relief of symptoms 1 day sooner than with placebo, but these early studies were performed in healthy young adults. Meta-analyses were performed on the data to look at high-risk individuals, including those 65 years of age and older. These studies showed that relief of symptoms came 2 days earlier for zanamivir but only 0.5 days earlier for oseltamivir in this high-risk population. Because of low numbers, it was unclear if treatment lowered the incidence of complications involving the lowering respiratory tract or hospitalization rates.

The Emerging Infections Program, which performs surveillance for influenza at hospitals in multiple states, evaluated the impact of antiviral treatment on influenza cases and found antivirals decreased the odds of extended care after hospital discharge and reduced length of stay. Similarly, a cohort study in Canada found that treatment with antivirals reduced mortality caused by influenza infection. Both these studies should be evaluated cautiously, as there were likely differences in the patients who received antiviral treatment (ie, prescription of these agents was at the discretion of the treating physician).

Peramivir underwent phase II trials under emergency use authorization during the 2009 influenza pandemic, as no other intravenous treatments were available. It was then approved for use in the United States by the US Food and Drug Administration.
in 2014. Phase III studies in Japan have shown peramivir to be noninferior to oseltamivir.27

According to recommendations from the US Centers for Disease Control and Prevention, neuraminidase inhibitors should be started within 48 hours of symptom onset for anyone 65 years of age or older. Hence it is recommended to start antivirals empirically until influenza testing results are available. The benefit of neuraminidase inhibitors after 48 hours of symptom onset is controversial.28,29

**PREVENTION**

**Vaccination**

The current influenza vaccines contain 15 mcg each of hemagglutinin of an A/H3N2, A/H1N1, and a B virus. Because of historically poor predictions of what influenza B lineage would circulate each year, many manufacturers have expanded the vaccine content to include a B virus from both lineages, creating what is known as a quadrivalent inactivated influenza vaccine (IIV4). The vaccine must be reformulated each year because of the changes in strain circulation.

Influenza vaccines were developed prior to World War II to prevent death and pneumonia in military recruits. In 1960 the US Surgeon General recommended the use of influenza vaccine in adults 65 years of age and older.30 This recommendation was made because of the high burden of morbidity and mortality in older adults. These recommendations were made not based on clinical trials showing clinical efficacy but rather, on extrapolation of data from trials in younger adults. Unfortunately for the same reasons that influenza is associated with more severe disease in older adults, older adults mount inadequate immunologic responses to influenza vaccine and have lower levels of clinical effectiveness. Older adults tend to have lower antibody responses to influenza vaccines.31 It is debated if this is because of poor immune responses or blunting of responses caused by prior influenza immunizations. Either way, antibody responses to influenza vaccines are lower than responses identified in younger adults. Similarly cell-mediated immune responses are lower.32 The degree to which these impact clinical effectiveness is not well-known.

Three randomized clinical trials (RCTs)33–35 have evaluated the efficacy of trivalent inactivated influenza vaccines in older adults. The first of the 3 RCTs used only ILI, and not laboratory-confirmed disease, as an endpoint.33 Because many illnesses also present with influenza-like symptoms (eg, other respiratory viruses circulating at the same time as influenza), the study was unable to show any vaccine effectiveness. The remaining 2 RCTs used serologic diagnosis of influenza as the efficacy endpoint. In the first of these 2 studies conducted by Govaert and colleagues,34 vaccine efficacy for serologically confirmed influenza was 56%, but this study was not adequately powered to examine the efficacy of the vaccine in those adults 70 years of age and older and only evaluated a healthy, independently living population. The second randomized study, which enrolled 653 subjects aged over 60 years old in Thailand,35 also used serologic evidence of infection as the endpoint. Overall, the relative risk reduction in the vaccinated population was 65% (95% CI, 16%–85%), but the study was also inadequately powered either to show a reduction in influenza in adults 70 years of age and older. Hence, no RCTs have been conducted to show influenza vaccine effectiveness in adults 70 years of age and older.

In order to overcome this lack of evidence, new effectiveness studies have been designed to evaluate the prevention of illness in older adults. These studies are observational but prospectively test patients presenting for medical care with an acute respiratory illness for influenza with PCR. To date, these studies show influenza vaccine
to be 40% to 60% effective for the prevention of hospitalization in adults 50 years of age and older when circulating and influenza vaccine strains are similar.\textsuperscript{5,8,36–41} Data remain lacking in the group 70 years of age and older.

In an attempt to overcome immune senescence that occurs in older adults, new influenza vaccines are being designed to protect this population from influenza. Currently there are 2 licensed influenza vaccines for use specifically in adults 65 years of age and older in the United States, a high dose vaccine and an MF59 adjuvanted vaccine. The first enhanced vaccine licensed for use in the United States was the high-dose influenza vaccine. The amount of hemagglutinin for each influenza strain was quadrupled, increasing the total amount of antigen from 45 mcg to 180 mcg. Early trials showed a significant antibody increase to influenza A (but not influenza B).\textsuperscript{42} A large phase IIIb/IV study showed a relative effectiveness of 24% for the high-dose versus the standard-dose influenza vaccine.\textsuperscript{43} A study using Medicare data looked at the relative vaccine effectiveness of the high dose compared with the standard dose during the 2012 to 2013 influenza season and found the high-dose vaccine to be 22% more effective.\textsuperscript{44} More recently, an adjuvanted influenza vaccine (aIIV) was licensed in the United States. This vaccine uses the traditional amount of hemagglutinin (45 mcg) but adds an adjuvant named MF59. This vaccine has been used for many years in Europe. A small randomized study was conducted for licensure, which showed similar but not superior antibody responses for the adjuvanted vaccine compared with the nonadjuvanted inactivated influenza vaccine.\textsuperscript{45} An observational study in Italy compared the effectiveness of the adjuvanted vaccine with a nonadjuvanted vaccine over 3 influenza seasons and found the risk of hospitalization for influenza or pneumonia was 25% lower for aIIV.\textsuperscript{46}

Attempts are currently underway to develop a universal vaccine that will work for any circulating influenza virus, so that patients would not necessarily need yearly vaccination nor would experts have to predict which influenza viral strains would need to be included in the following year’s vaccine. Until the development of such a vaccine, patients (and health care workers) need yearly vaccination. Table 1 lists the currently available vaccines licensed in the United States.

Influenza vaccine is usually given early in the fall to allow for the body to make an immune response prior to influenza season. As vaccine is introduced earlier and earlier each year, concerns have arisen about waning immunity, meaning that the protection provided by the vaccine may wane prior to the cessation of influenza circulation. Unfortunately there is little evidence about the true duration of protection, leaving many providers wondering when to give vaccine. Despite concerns about vaccinating too early, it is important not to miss an opportunity to vaccinate all older adults.

\textit{Herd Protection}

One of the most effective ways to prevent an individual from an infectious agent is to vaccinate the population. Multiple studies\textsuperscript{47–50} have shown that vaccinating health care workers in nursing homes provides protection from influenza infection in patients. These studies have compared nursing homes where employees are vaccinated with nursing homes where employees are not vaccinated. The largest of these studies had 22 long-term care facilities. The patient mortality in the facilities without vaccination of employees was 15.3%, while the mortality of patients in facilities that vaccinated employees was 11.2%.\textsuperscript{47} This suggests that the introduction of influenza into a facility occurred from the staff, but other sources, such as visitors, cannot be excluded. Hence, vaccination of employees likely blocks at least some introduction of influenza into the facility. One ecologic study has hinted that immunization of
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Currently licensed influenza vaccine formulations in the United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H3N2</td>
<td>Inactivated Influenza Vaccine – Trivalent (IIV3)</td>
</tr>
<tr>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>x</td>
</tr>
<tr>
<td>Either B/Victoria or B/Yamagata</td>
<td>x</td>
</tr>
<tr>
<td>Both B/Victoria &amp; B/Yamagata</td>
<td>x</td>
</tr>
<tr>
<td>Egg Culture</td>
<td>x</td>
</tr>
</tbody>
</table>
younger adults in the community may also protect older adults from influenza infection.51

**Antiviral Medications**

Antiviral medications may be used for treatment and prevention of influenza. Both oseltamivir and zanamivir have been licensed for prophylaxis.

The use of antiviral medications is ideal in the setting of outbreaks in long-term care facilities. An RCT compared the impact of treating individuals with influenza versus treating the infected individuals and giving prophylactic doses to noninfected residents. With the use of prophylactic treatment, there was a reduction in the duration of outbreaks (24 vs 11 days) and a reduction in the attack rate (36% vs 23%).52

One study used daily oseltamivir in a blind RCT to prevent outbreaks from occurring in long-term care facilities.53 This study included 572 volunteers from 31 centers and found a reduction in laboratory-confirmed clinical cases (4.4% vs 0.4%).

If a case of influenza is identified in a long-term care facility, all patients should receive antiviral prophylaxis; vaccination of staff and residents should be completed, and appropriate infection control policies (droplet precautions) should go into effect.

**SUMMARY**

Influenza causes significant morbidity and mortality in older adults, and prevention with vaccination and antiviral medications is important to reduce the morbidity and mortality of influenza. Future research will need to create an influenza vaccine that not only is effective regardless of the circulating strain but creates a protective response in an aging immune system.

**REFERENCES**


