

Influenza in Older Patients: A Call to Action and Recent Updates for Vaccinations

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Influenza is an acute respiratory infection found worldwide and known to infect humans, other mammals, and birds. In the Northern Hemisphere, outbreaks of influenza occur seasonally, primarily from December to March. It is a self-limiting disease in most individuals. The classic acute flu-like symptoms develop in about 50% of people and include fever (usually 101°-102° F), myalgia, sore throat, nonproductive cough, and headache.¹ It is transmitted via respiratory droplets from sneezing and coughing, starting approximately 1 to 2 days before symptoms appear up to 5 to 10 days later, but the infection may last longer in very young, elderly, and immunocompromised persons. Secondary complications, such as pneumonia, bronchitis, and sinus and ear infections, as well as exacerbations of chronic medical conditions, are sources of considerable morbidity and mortality.¹

Adults 65 years or older represent a large at-risk population. These patients account for most seasonal influenza-related hospitalizations and related complications.¹ Most seasonal influenza-related deaths occur in adults 65 years or older. While the percentage of US adults 65 years or older receiving an influenza vaccination is higher than in younger age groups, it remains that only 65.3% of these adults received a flu vaccination in the last 12 months, leaving about 35% of all older adults unprotected against influenza.¹

Influenza From Then to Now

Pandemics are worldwide events; epidemics and outbreaks are localized. The first recognized pandemic occurred in 1580, spreading from Asia to Asia Minor, North Africa, Europe, and North America.² The pandemic of 1918 sickened half the world's population and killed approximately 50 million people, about 3% of the world's population.² Other pandemics of the 20th century include the 1957 Asian flu and the 1968 Hong Kong flu; the most recent pandemic, the swine flu, occurred in 2009. In the latter, most fatalities occurred in Africa (an estimated 151,700 people) and Southeast Asia (an estimated 575,400).³

Although available vaccines reduce the prevalence and risk of contracting influenza, vaccination uptake is not optimal, leaving many millions at risk of infection. Each year, the CDC estimates the impact of influenza on the US population, based on models that

ABSTRACT

Influenza affects millions of people in the United States each year. Older patients are particularly at risk for infection, hospitalization, and death due to influenza-related complications, such as pneumonia. One of the best ways to avoid becoming ill is to have the annual influenza vaccination. Unfortunately, immunization rates are poor in the older adult population, at about 65% each year. Vaccine effectiveness in this population is reduced because of lower seroconversion rates that arise from poorer immunologic response to vaccination. Several new influenza vaccines that have been introduced to the market in recent years attempt to boost immune response, including high-dose formulations and adjuvanted and recombinant vaccines. Managed care pharmacists need to understand the utility of these new agents in populations 65 years or older. This supplement highlights the impact of influenza on older patients, the features of new vaccine preparations, and the economic burden of influenza.

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For author information and disclosures, see end of text.

incorporate reported death rates (influenza and influenza-related), vaccination rates, and vaccine effectiveness, to arrive at ranges of persons affected, persons hospitalized, deaths, and illness averted. These ranges can be quite large, depending on the flu season. Since 2010, there have been 9.2 million to 35.6 million cases of influenza in the United States, causing an estimated 140,000 to 710,000 hospitalizations and 12,000 to 56,000 deaths in each.¹ The total economic burden of annual influenza epidemics using projected statistical life-values is nearly \$100 billion.⁴

Severity of Influenza in Older Patients

The term influenza was first used in the scientific literature in 1650 and the first influenza virus was isolated in 1931.² There is now a much greater understanding of influenza, which has allowed us to develop vaccines and the tools necessary to care for the most severely affected patients.

Populations at Risk

For most people, influenza is a relatively mild illness that usually does not require extensive medical care. However, some groups of people are at higher risk of developing influenza-related complications that require hospitalization and may lead to death. People in these groups include infants and young children 6 months to 5 years, older adults (≥ 65 years of age), pregnant women, residents of long-term care facilities, Native Americans, and those with certain chronic medical conditions (eg, asthma, diabetes, heart disease).¹ The focus in this supplement will be on elderly patients.

Elderly Populations

During a typical influenza season, most people infected by the virus recover in 3 to 10 days. However, elderly persons bear the greatest burden of morbidity and mortality of any group, with 54% to 70% of seasonal influenza-related hospitalizations and 71% to 85% seasonal influenza-related deaths.¹

Older patients are less likely to display classic influenza symptoms than are younger patients. Fever is often not present. Instead, many older patients present with exacerbations of pre-existing comorbidities, such as dyspnea or cough. In a survey of laboratory-documented influenza in veterans older than 50 years with chronic obstructive pulmonary disease (COPD), respiratory symptoms (cough, sputum production, and dyspnea) occurred in more than 90% of patients, fever in 68%, and myalgias in 81%.⁵

The elderly population is afflicted by significant comorbidities, many of which are, themselves, risk factors for influenza-related complications. These include chronic lung disease (eg, COPD), heart disease (eg, heart failure and coronary artery disease), endocrine disorders (eg, diabetes), kidney and liver disorders, weakened immune system due to disease or medication (eg, cancer therapy, chronic steroid use), and extreme obesity (body mass index ≥ 40).¹

Immunosenescence

With advancing age comes declining systemic immunity.⁶ Immunosenescence describes the age-related decline of both innate and adaptive immunity, leaving the person more susceptible to disease caused by pathogens, including influenza and those causing influenza-related complications. Immunosenescence is suspected to be the cause of the counter-intuitive observation that, in pandemics, younger people are afflicted with higher mortality and morbidity. It has been postulated that younger people, with a more robust immune system, produce a stronger reaction and trigger a life-threatening cytokine storm, although older people do not.² Thus, although older people are less likely to die from influenza, they are more likely to become infected in nonpandemic years. Unfortunately, influenza infection opens the door to other, opportunistic infections that, ultimately, are responsible for most deaths from influenza during both pandemics and seasonal disease spread.

Influenza Virus

Influenza is a collection of related *Orthomyxoviridae* viruses with varying characteristics, such as preferred host. Four types exist: Type A infects humans, swine and other mammals, and birds; types B and C infect humans; and type D affects cattle and does not affect humans.¹ Types A and B are associated with considerable morbidity and mortality in humans, while type C typically causes only mild symptoms.

Structure and Nomenclature

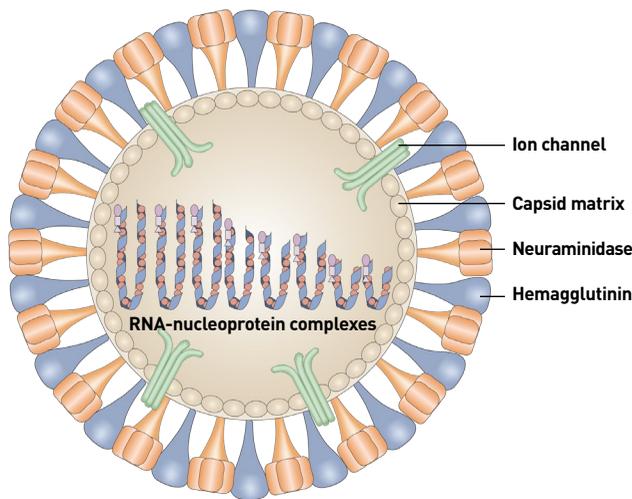
Influenza virus particles have a capsid composed of lipid and protein, surrounding a core of RNA and protein (**Figure 1**).⁷ The capsid proteins are primarily hemagglutinin and neuraminidase, which contain the antigenic determinants.

Subtypes of influenza type A viruses are distinguished by the specific isoform of hemagglutinin and neuraminidase on the virion surface. There are 18 different hemagglutinins (H1-H18) and 11 different neuraminidases (N1-N11).¹ The H/N designation gives rise to the familiar "H1N1," "H3N2," and similar names of these viruses. The full name for an influenza virus includes the antigenic type (A, B, C, D), lineage or original host species (eg, bird, swine, bat, with the exception of "human," which is never listed), geographic origin (if known), strain number (ie, sub-subtype), year the virus was isolated, and the H/N subtype designation (**Figure 2**).^{1,8}

Influenza Genome

Influenza is a segmented RNA virus. Eight different RNA strands are within each virion, much like the human nucleus has 23 different chromosomes.⁷ Each RNA strand encodes 1 of 8 influenza genes that produce 11 proteins. The segmented nature of the influenza genome allows for shuffling of genes, when multiple influenza

FIGURE 1. Structure of Influenza Virus Particles⁷



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viruses are present at the same time within a cell. This can occur in numerous hosts, such as birds and swine. The resulting virus has never been seen in most hosts. This feature is critical to the high-level virulence seen in epidemics and pandemics. The Spanish flu of 1918 was a product of a swine hemagglutinin inserted into a human virus.

“Drift” Versus “Shift”

Currently circulating influenza A viruses include the H1N1 and H3N2 subtypes and circulating B virus lineages include Yamagata and Victoria. However, influenza changes and evolves readily. Small changes are known as “antigenic drift” and result from, for instance, single nucleotide changes in the influenza genome.¹ Immunologically, viruses that experience antigenic drift will be very similar to the original virus and are likely to have similar (but not identical) antigenic properties. A hemagglutinin 3 can drift and become a hemagglutinin 3 variant. An immune system that has seen 1 virus could possibly react against the new virus (ie, “cross-protection”).¹

With each incremental drift, the likelihood of cross-protection is reduced. Eventually, enough drift occurs that a person’s immune system will not recognize the newest version of the virus.¹ When this happens, the person can become ill again with the same H/N influenza variant.

Antigenic shift, on the other hand, is a large change in the genome of the virus; it occurs infrequently.¹ These changes typically result in new and exceptionally virulent strains of influenza, and they can cause pandemics. Antigenic shift involves reassembly of the virus from 1 or more types of influenza into a chimeric virus, having parts from multiple sources.

Each year, the CDC analyzes more than 1 million patient specimens and sequences the genomes of 6000 viruses to prepare up to 50 viruses for possible use in vaccine production.¹ They then take their best reasoned guess of which viruses will be dominant the following influenza season.

Complications of Influenza Infection

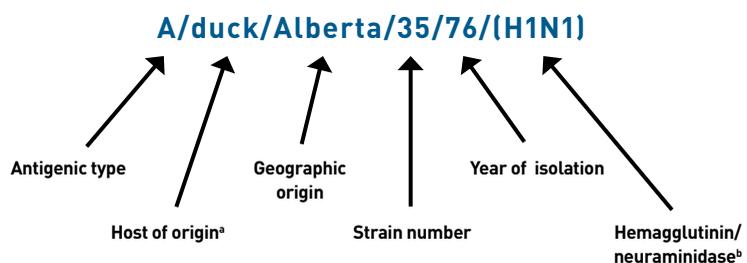
Influenza infection is characterized as either uncomplicated, meaning that illness is confined to symptoms of influenza alone, or complicated, meaning that secondary illness or infection sets in.⁹

Pneumonia

Pneumonia is the most common serious complication. As a result of weaker immunity and higher incidence of comorbidities, the elderly are more likely to be afflicted with influenza-related complications, particularly pneumonia.¹ Factors associated with an increased risk of developing pneumonia include age 75 years or older, nursing home residence, chronic lung disease, immunosuppression, and asthma.¹⁰ Patients with an influenza infection and pneumonia were significantly more likely to require intensive care unit (ICU) admission (27% vs 10%) and mechanical ventilation (18% vs 5%), and to die (9% vs 2%), as compared with patients without pneumonia.

Pneumonia may be caused by the influenza virus, another virus (eg, respiratory syncytial virus), or bacteria (eg, *Streptococcus*, *Staphylococcus*). Primary influenza viral pneumonia can develop rapidly, within 2 to 5 days of the onset of symptoms, and may require intubation and mechanical ventilation.⁹ Influenza and bacterial coinfection occur in 11% to 35% of patients.¹¹ The most

FIGURE 2. Influenza Virus Nomenclature¹



^aNot included for human-origin viruses.
^bProvided for influenza A type viruses only.

commonly encountered bacteria are *Streptococcus pneumoniae* and *Staphylococcus aureus*, accounting for 35% and 28% of identified coinfecting bacteria, respectively. Other pathogens encountered include *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Mycoplasma pneumoniae*. Secondary bacterial pneumonia should be suspected in patients who initially improve, but then worsen within 2 weeks of the onset of influenza symptoms.⁹

Less Common Complications

Less common serious complications of influenza infection occur in extrapulmonary sites.¹² Most often, extrapulmonary complications are associated with the acute phase of the infection. Weeks later, other symptoms, particularly those that affect the central nervous system (eg, Guillain-Barré syndrome, encephalitis, Reye syndrome), and exacerbations of pre-existing comorbidities (eg, myocarditis/pericarditis) may follow. The possibility of late-onset sequelae remains controversial.

Myocarditis has been reported in approximately 0.4% to 13% of hospitalized adult patients with documented influenza, based on elevation of cardiac enzymes and echocardiographic findings.¹³ In fatal influenza infections, myocarditis and myocyte necrosis have been observed in approximately 30% to 50% of patients at autopsy.¹² However, it appears to be more common among younger patients, with 68% of cases in patients younger than 40 years.

Neurologic complications are rare and affect mainly children, although they can affect adults.¹² People of Asian/Pacific Islander descent appear to be more susceptible than white, non-Hispanic patients (occurrence rate per million persons of 12.79 vs 3.09, respectively).¹⁴

Other complications of influenza infection have been noted, including rhabdomyolysis, ocular manifestations (eg, conjunctivitis, retinopathy, uveal effusion syndrome, optic neuritis), acute kidney injury, hepatic injury, hematologic complications, and complications related to diabetes.¹² However, the mechanisms linking these complications with influenza infection are not clear.

The Burden of Illness of Influenza in Older Populations

It is important that older patients receive annual influenza vaccination.^{9,15} Vaccines are a proven method of reducing the spread of influenza.¹

The CDC recommends that all persons older than 6 months receive the vaccine. Importantly, healthcare workers should receive the vaccine to reduce the spread of the virus, particularly if they care for at-risk patients (eg, long-term care residents).¹

Rate of Vaccination

Seasonal influenza is associated with significant morbidity and mortality. From 2010-2011 to 2015-2016, influenza-related hospitalizations in the United States ranged from a low of 140,000 (during 2011-2012) to a high of 710,000 (during 2014-2015).¹ The hospitalization rate in the 2016-2017 season was 65.0/100,000 for all age groups, and 290.5/100,000 for adults 65 years or older.¹⁶

Mortality data are not typically available for 3 years after an influenza season because of the need to model the data. Relying on death certificates for enumerating mortality has several problems, including incomplete and inaccurate reporting. Data modeling circumvents these deficits. The CDC estimates that, between 2010 and 2014, there were 12,000 to 56,000 deaths from seasonal influenza.¹

Vaccine Coverage

The global target vaccination coverage rate for persons 65 years or older is 75%; in the United States, it is 90%.¹⁷ This target is rarely met in the industrialized world, and the developing world has even poorer coverage.¹⁷ The influenza vaccination coverage rate in the United States for the 2016-2017 season was 65.3% in adults 65 years or older, representing an increase of 1.9% over the previous year (Figure 3).¹ However, 2015-2016 saw the lowest coverage rate since 2010. The average coverage over the past 7 seasons (2010-2011 to present) has remained at 65.4% (range, 63.4%-66.7%).¹

FIGURE 3. Vaccination Coverage Rates in the United States¹

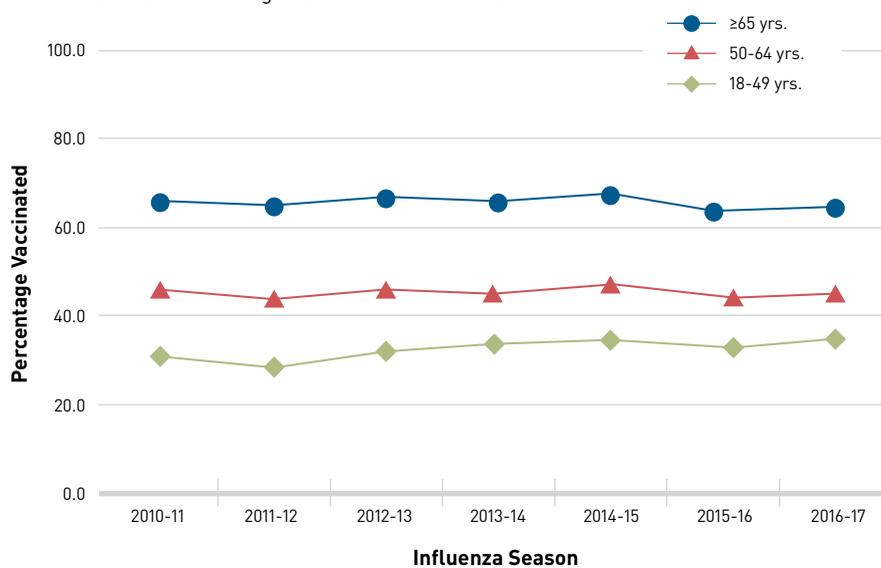
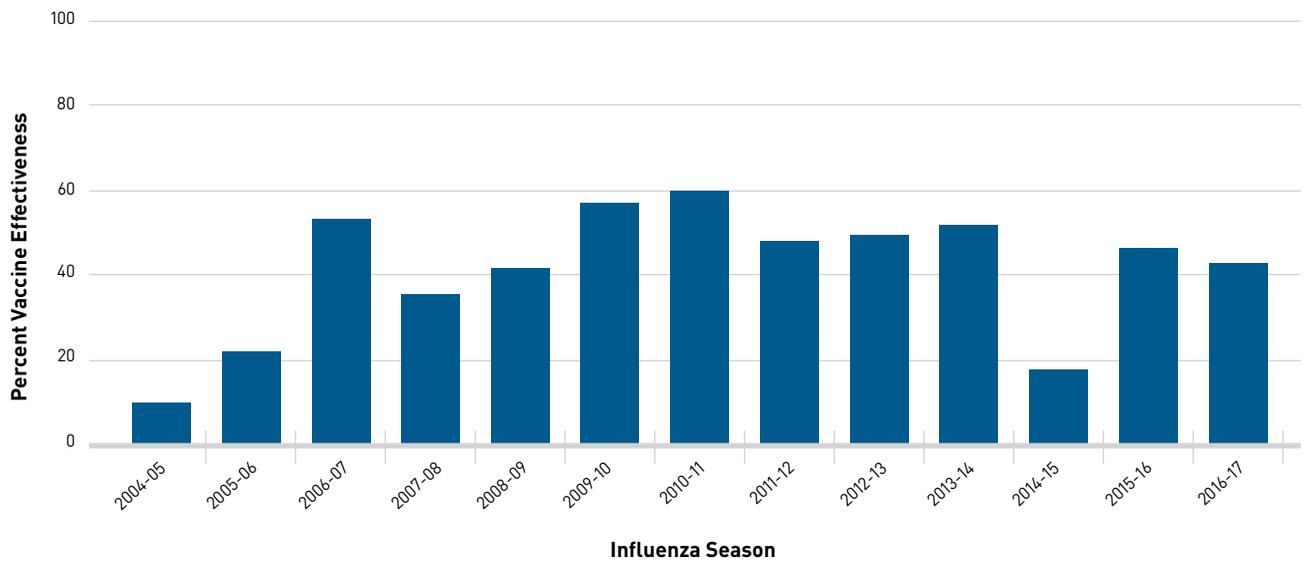


FIGURE 4. Adjusted Overall Vaccine Effectiveness in the United States¹



Significant barriers to full coverage exist.¹⁸ Lack of confidence in the vaccine and personal complacency are major reasons people skip vaccination. Vaccine avoidance is higher among people with negative attitudes toward vaccines and health authorities and those who perceive vaccines as ineffective. Some people are worried about the safety of vaccines (eg, mercury in thimerosal), perceive the threat of illness as low (eg, generally healthy people), or do not receive encouragement from healthcare providers to be vaccinated. On the other side, people with positive attitudes toward influenza vaccines, high perceived utility of vaccination, cues to action (eg, peers and healthcare providers), and previous influenza vaccinations are more likely to be vaccinated.

Strategies proven to increase adult vaccination rates include screening all patients for immunization status at each visit, educating patients about the importance of vaccination, and providing a strong recommendation to receive needed vaccines. In addition, systems can facilitate vaccination rates by reminding providers about needed vaccines and using alerts to schedule follow-up doses for multidose series.

Vaccine Effectiveness

Because of genetic drift and constant antigenic changes on the virus, people should receive the influenza vaccine each year for optimal protection.¹ Vaccine production requires about 9 months to build adequate reserves. The CDC makes a best educated guess at which strains will be prominent in the next influenza season. Often, this guess is a good match between viruses in the vaccine and that season’s circulating viruses. However, sometimes, the

vaccine and circulating viruses are mismatched to a degree. This results in reduced vaccine effectiveness. Over the past decade, the overall vaccine effectiveness has hovered in the 40% to 55% range, although some years have been better or worse than others (Figure 4).¹ For instance, the 2014-2015 season was particularly bad, with vaccine effectiveness of less than 20%. The influenza vaccine is composed of 3 or 4 viral components. Even if the vaccine is not matched directly to the circulating viruses of that season, it can provide benefits, including reduced severity, due to cross-protection, and protection against viruses that were successfully matched in the vaccine. In an analysis of the 2013-2014 influenza season (the most recent for which data are available), vaccination reduced the odds of in-hospital deaths (adjusted odds ratio [aOR], 0.39; 95% CI, 0.17-0.66), ICU admission (aOR, 0.63; 95% CI, 0.48-0.81), length of ICU stay (adjusted relative hazard [aRH], 1.34; 95% CI, 1.06-1.73), and hospital length of stay (aRH, 1.24; 95% CI, 1.13-1.37) in patients 65 years or older.¹⁹ Becoming infected with influenza does not prevent a person from becoming infected the next year, or even in the same season; again, this is due to genetic drift or infection with an unrelated influenza virus. The influenza vaccine does not protect people against other respiratory viruses and illnesses.

Vaccine Timing

Ideally, individuals should be vaccinated several weeks before the influenza season because immunity does not build to sufficient levels until 2 weeks after vaccination. The CDC recommends that people be vaccinated before influenza virus is circulating in the community, and by the end of October at the latest. Getting vaccinated

later in the season can be beneficial, but it delays protection and could result in influenza infection.¹

A recent examination of vaccine effectiveness among enrollees (all ages) in the US Influenza Vaccine Effectiveness Network for the 2011-2012 through 2014-2015 influenza seasons supports the notion that effectiveness wanes with time.²⁰

- Adjusted vaccine effectiveness against influenza A (H3N2) virus infection decreased from a maximum of 35% at 14 days post vaccination and reached zero at 158 days (7% decline per 30-day period)
- Adjusted vaccine effectiveness against influenza A (H1N1) pdm09 virus infection decreased from a maximum of 80% at 14 days post vaccination and reached a minimum of 37% at 128 days (6%-11% decline per 30-day period)
- Adjusted vaccine effectiveness against influenza B virus infection decreased from a maximum of 59% at 14 days post vaccination and reached a minimum of 23% at 180 days (7% decline per 30-day period)

There is concern that immunity in elderly persons declines more rapidly than in younger people, and that it may not last through the entire season.²¹⁻²³ However, this may reflect a poorer primary response to vaccination.²¹ Skowronski et al reviewed 8 studies, results of which reported seroprotection rates in persons 65 years or older.²² They found that adequate seroprotection rates were maintained 4 months or longer, by Committee for Proprietary Medicinal Products standards, in all 8 of the studies reporting for the H3N2 component and in 5 of the 7 studies reporting for the H1N1 and B components. Their review suggested that the primary response to vaccination was of greater predictive importance than secondary antibody decline post vaccination. For those people who seroconverted for the H3N2 and H1N1 vaccine components, seroprotection rates of 70% to 100% were observed in 2 studies at 4 months, 2 studies at 5 months, and 4 studies at longer than 6 months. Less consistent seroprotection against the B component was observed. Seroconversion was inversely correlated with preimmunization titers but not with age.²²

Toolkits for Expanding Coverage

The CDC has many toolkits to assist healthcare personnel and institutions improve vaccination coverage.¹ These include:

- General campaign materials for employers, healthcare personnel, and the public
- Toolkits for establishing and improving an influenza vaccination program
- Cultural and language resources
- Guidance for promoting influenza vaccination in a facility

These materials are available as Web-based materials, printable materials, and/or videos/podcasts.²⁴ The toolkits include influenza fact sheets for employers, healthcare personnel, and patients; best practice guidance documents and checklists for patient safety and vaccine effectiveness; and forms and educational content in a variety of languages.

Influenza Vaccination Products for Use in Older Adults

Older patients typically do not mount as strong an immune response to vaccines as do younger patients. Even with vaccination, older people are less likely to achieve full protection. In a quantitative review of 31 studies that compared antibody responses to influenza vaccines in adults, younger adult populations achieved 70% to 90% seroconversion and seroprotection rates, and older populations achieved considerably reduced rates of approximately 17% to 53%.²⁵ The reason for this is unknown, but immunosenescence and blunting of immune response due to repeated prior immunization have been put forth as hypotheses.²⁶ Regardless of the reason, there remains a need for improved vaccine seroconversion and seroprotection among older patients.

This section will focus on the delivery of influenza vaccine to adults 65 years or older. The package inserts of vaccine formulations may contain additional information relevant to the administration of the product to children and other special populations. The reader is encouraged to consult this information for people younger than 65 years, as significant differences may exist between populations.

2017-2018 Advisory Committee on Immunization Practices Influenza Vaccine Recommendations

The CDC recommends use of injectable vaccines, either inactivated virus or recombinant influenza vaccines.¹ The nasal spray influenza vaccine is not recommended for any groups of people during the 2017-2018 influenza season, according to the Advisory Committee on Immunization Practices (ACIP).²⁷ The nasal spray vaccine is indicated for patients 2 to 49 years of age in other years. Influenza vaccines are composed of either 3 or 4 components that are intended to provide immunity to 2 A type and 1 or 2 B type influenza viruses. Of influenza A type viruses that were sequenced in the 2016-2017 season (77.9% of all influenza viruses), 97.2% were influenza A (H3N2) viruses and 2.8% were influenza A (H1N1)pdm09 viruses (the virus that caused the 2009 pandemic). Of influenza B type viruses that were sequenced, 71.2% belonged to the B/Yamagata lineage and 28.8% to the B/Victoria lineage.¹⁶

For the 2017-2018 season, influenza vaccines have been updated to better match circulating viruses.¹⁶ The FDA Vaccines and Related Biologic Products Advisory Committee has recommended that the 2017-2018 influenza trivalent vaccine to be used in the United States contain an A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Hong

TABLE. Types of Influenza Vaccines¹

Influenza Vaccine Name	Presentation	Age Indication
Trivalent influenza vaccines		
Inactivated trivalent vaccine (IIV3), standard dose		
Afluria	0.5 mL prefilled syringe	≥5 years
	5.0 mL multidose vial	≥5 years (by needle/syringe)
		18-64 years (by jet injector)
Fluvirin	0.5 mL prefilled syringe	≥4 years
	5.0 mL multidose vial	≥4 years
Inactivated trivalent vaccine (IIV3-HD), high dose		
Fluzone High-Dose	0.5 mL prefilled syringe	≥65 years
Adjuvanted inactivated trivalent vaccine (aIIV3), standard dose		
Fluad	0.5 mL prefilled syringe	≥65 years
Recombinant trivalent vaccine (RIV3)		
Flublok	0.5 mL single-dose vial	≥18 years
Quadrivalent influenza vaccines (all standard dose)		
Inactivated quadrivalent vaccines (IIV4)		
Afluria Quadrivalent	0.5 mL prefilled syringe	≥18 years
	5.0 mL multidose vial	≥5 years (by needle/syringe)
		18-64 years (by jet injector)
Fluarix Quadrivalent	0.5 mL prefilled syringe	≥3 years
FluLaval Quadrivalent	0.5 mL prefilled syringe	≥6 months
	5.0 mL multidose vial	≥6 months
Fluzone Quadrivalent	0.25 mL prefilled syringe	6-35 months
	0.5 mL prefilled syringe	≥3 years
	0.5 mL single-dose vial	≥3 years
	5.0 mL multidose vial	≥6 months
Inactivated quadrivalent vaccine (ccIIV4), cell culture-based		
Flucelvax Quadrivalent	0.5 mL prefilled syringe	≥4 years
	5.0 mL multidose vial	≥4 years
Inactivated quadrivalent vaccine (IIV4), intradermal		
Fluzone Intradermal Quadrivalent	0.1 mL single-dose microinjection system	18-64 years
Recombinant quadrivalent vaccine (RIV4)		
Flublok Quadrivalent	0.5 mL prefilled syringe	≥18 years

Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like (B/Victoria lineage) virus. The quadrivalent vaccine is to contain the viruses in the trivalent vaccine, plus a B/Phuket/3073/2013-like (B/Yamagata lineage) virus. The major difference this year from last is the updating of the A (H1N1) viral component.

Available Vaccine Products

The Table lists the various types of available vaccine products. Inactivated influenza vaccines (IIV) have 15 mcg of each HA antigen (45 mcg total in trivalent, and 60 mcg total in quadrivalent vaccines).²⁷ Adults 65 years or older may receive any age-appropriate influenza vaccine (Table). This may include standard- or high-dose, trivalent (IIV3) or quadrivalent (IIV4), and adjuvanted (aIIV) or unadjuvanted vaccine. Sometimes, standard-dose IIV3 is referred to as “IIV3-SD,” when there is a need to distinguish it from the high-dose (IIV3-HD) vaccine. Single-dose vials do not contain thimerosal, although multidose vials most often do. All influenza vaccines intended for adults 65 years or older are delivered via intramuscular injection.

Trivalent Influenza Vaccines

Influenza vaccines were developed for use by the US military and, in the early 1960s, the use was expanded to high-risk populations, including adults 65 years or older.²⁸ Traditionally, these vaccines have 3 components (ie, trivalent): 2 A-type viral products and 1 B-type. To date, data from adequately powered trials have shown vaccine effectiveness of 40% to 60% in adults 50 years or older when circulating and influenza vaccine strains are similar.²⁶ However, adequately powered trial data are lacking for the cohort of adults 65 years or older.

TRIVALENT, STANDARD-DOSE, INACTIVATED INFLUENZA VACCINES

A standard-dose, trivalent, inactivated influenza vaccine (Afluria [IIV3]) is available for people 5 years or older.²⁹ It is purified from the allantoic fluid of embryonic chicken eggs over a sucrose density gradient, inactivated with β-propiolactone, and disrupted with mild detergent (sodium taurodeoxycholate) to produce a “split-virion.” The vaccine contains greater than trace amounts of detergents, ovalbumin, antibiotics (neomycin sulfate, polymyxin B), and β-propiolactone.

Another standard-dose, trivalent, inactivated influenza vaccine (Fluvirin [IIV3]) available is for people 4 years or older.³⁰ The antigens are purified from influenza virus produced in eggs. Hemagglutinin and neuraminidase antigens are purified by zonal gradient centrifugation. Trace amounts of egg and viral proteins, antibiotics (neomycin sulfate, polymyxin B), detergents, polymers used during purification, and thimerosal may remain.

TRIVALENT, STANDARD-DOSE, RECOMBINANT INFLUENZA VACCINES

The recombinant, trivalent, standard-dose influenza vaccine (Flublok [RIV3]) is an egg-free, recombinant hemagglutinin product, produced in cell culture (insect cells) grown in serum-free media, that is available for individuals 18 years and older.³¹ Hemagglutinin protein from each of the 3 influenza strains is purified and mixed to provide 45 mcg of each (135 mcg total). This product is of significant benefit to those persons with severe egg allergy, defined as symptoms greater than hives alone after influenza vaccination (eg, bronchospasm). It is free of infectious influenza virus, antibiotics, thimerosal, preservatives, gelatin, and latex.

High-Dose, Adjuvanted, and Quadrivalent Influenza Vaccines

To circumvent deficient immunity in older people, vaccine manufacturers have created high-dose and adjuvanted vaccines, with the goal of provoking a stronger immune response.

TRIVALENT, HIGH-DOSE, INACTIVATED INFLUENZA VACCINES

A trivalent, inactivated, split-virion, high-dose influenza vaccine (Fluzone High-Dose [IIV3-HD]) is indicated for use in adults 65 years or older.³² It is produced in eggs and purified through sucrose density gradient centrifugation. High-dose formulations contain 60 mcg hemagglutinin of each influenza strain, as compared with 15 mcg hemagglutinin of each strain in standard-dose influenza vaccines. IIV3-HD vaccines induce substantially greater antibody responses and better protection against influenza and influenza-associated hospitalization than IIV3-SD.³³ In a study of 31,989 participants, 1.4% of those receiving the high-dose formulation had laboratory-confirmed influenza, compared with 1.9% of those receiving the standard dose.³² Persons receiving the high-dose formulation also experienced higher hemagglutination-inhibition (HAI) titers and reduced incidence of serious adverse effects.³² It has been suggested that, due to improved coverage and prevention of illness, IIV3-HD may provide cost savings compared with IIV3-standard dose in older patients.^{34,35}

TRIVALENT, STANDARD-DOSE, INACTIVATED, ADJUVANTED INFLUENZA VACCINES

A trivalent, standard-dose, inactivated, adjuvanted influenza vaccine (Fluad [aIIV3]) is available for use in patients 65 years or older.³⁶ It is produced by the same methods as Afluria. In addition, the adjuvant MF59C.1 is included. MF59C.1 is a squalene-based, microfluidized (oil in water) emulsion.³⁷ It activates monocyte transition to dendritic cells, recruitment of antigen-presenting cells, and antigen uptake. A pooled analysis of case-controlled studies found an adjusted vaccine effectiveness of 51% for adjuvanted trivalent influenza vaccination, with an effectiveness against laboratory-confirmed

influenza of 61.1%.³⁷ The MF59C.1 adjuvanted trivalent vaccine reduced hospitalizations (aRH, 0.75) and laboratory-confirmed influenza (aOR, 0.37), as compared with nonadjuvanted vaccine.

QUADRIVALENT, STANDARD-DOSE, INACTIVATED INFLUENZA VACCINES

A quadrivalent, standard-dose, inactivated influenza vaccine (Afluria Quadrivalent [IIV4]) is available, manufactured by the same methods as Afluria trivalent.³⁸ It is approved for patients older than 5 years.

A second split-virion, quadrivalent, inactivated influenza vaccine (Fluzone Quadrivalent [IIV4]) is approved for use in patients 6 months or older.³⁹ It is produced in eggs, purified in a sucrose gradient, inactivated with formaldehyde, and disrupted with detergents. Greater than trace amounts of ovalbumin, formaldehyde, and detergents may remain. Unlike most influenza vaccines, antibiotics are not used during the manufacture of this vaccine.

There is a split-virion, quadrivalent, inactivated influenza vaccine (Fluarix Quadrivalent [IIV4]) that is approved for use in patients 3 years or older.⁴⁰ It is produced in eggs, purified by zonal sucrose gradient, and disrupted with sodium deoxycholate and formaldehyde. Greater than trace amounts of residual detergents, hydrocortisone, ovalbumin, and formaldehyde may remain.

Another split-virion, inactivated, quadrivalent influenza vaccine (FluLaval Quadrivalent [IIV4]) is available for use in patients 6 months or older.⁴¹ It is produced in eggs and inactivated by formaldehyde and ultraviolet light and disruption with sodium deoxycholate. Greater than trace amounts of ovalbumin, formaldehyde, and detergents may remain. It is also free of antibiotics.

QUADRIVALENT, STANDARD-DOSE, RECOMBINANT, INACTIVATED INFLUENZA VACCINES

There is a recombinant, quadrivalent, standard-dose, inactivated influenza vaccine (Flublok Quadrivalent [RIV4]) that is an egg-free, recombinant hemagglutinin product produced in cell culture.⁴² People with egg allergies may receive this or the trivalent influenza vaccine (Flublok). It is free of infectious influenza virus, antibiotics, thimerosal, preservatives, gelatin, and latex. Results of a single study involving 8963 adults (mean age, 62.5 years) during the 2014-2015 influenza season showed that the recombinant vaccine (RIV4) was more efficacious than the quadrivalent, inactivated virus vaccine (IIV4), and that people receiving it were 30% less likely to become ill with laboratory-confirmed influenza.^{42,43} However, the FDA did not allow the manufacturer to claim superiority of this RIV4 over other IIV4 vaccines.⁴⁴

QUADRIVALENT, STANDARD-DOSE, INACTIVATED INFLUENZA VACCINES PRODUCED IN CELL CULTURE

A recombinant, quadrivalent, standard-dose inactivated influenza vaccine (Flucelvax Quadrivalent [RIV4]) that is produced in cell

culture is an egg-free, recombinant hemagglutinin product produced in immortalized Madin-Darby Canine Kidney cells.⁴⁵ It is approved for use in people 4 years or older. It does not contain ovalbumin, antibiotics, or natural latex.

QUADRIVALENT, STANDARD-DOSE, INTRADERMAL, INACTIVATED INFLUENZA VACCINES

There is an intradermal, quadrivalent, standard-dose influenza vaccine (Fluzone Intradermal Quadrivalent [IIV4]) that is approved for people aged 18 through 64 years.⁴⁶ Viral particles are produced in chicken eggs, purified in sucrose gradients, inactivated with formaldehyde, and disrupted with detergents. It contains 9 mcg of each hemagglutinin (36 mcg total) and is injected intradermally. The same level of seroprotection may be obtained with less antigen through intradermal vaccination, compared with vaccination via the intramuscular route, due to the greater concentration of immune cells and a more robust immune response to antigen.⁴⁷ Greater than trace amounts of formaldehyde and detergents may remain. It is latex-free.

Vaccination in Older Patients with Comorbidities

The population of older patients with comorbidities is at high risk for complications due to influenza. These patients often have pulmonary and cardiac deficits. In this at-risk population, high-dose vaccination appears to be safe and efficacious. Over a 6- to 8-month period after receiving either high- or standard-dose IIV3 influenza vaccination, these vaccine efficacy results against laboratory-confirmed influenza-like illness were noted.⁴⁸

- Age: 19.7% (95% CI, 0.4%-35.4%) for participants 65 to 74 years and 32.4% (95% CI, 8.1%-50.6%) for those 75 years or older
- Comorbidities: 22.1% (95% CI, 3.9%-37.0%) for participants with 1 or more high-risk comorbidity and 23.6% (95% CI, -3.2% to 43.6%) for those with 2 or more high-risk comorbidities
- Frailty: 27.5% (95% CI, 0.4%-47.4%) for persons with 1 frailty condition, 23.9% (95% CI, -9.0% to 47.2%) for those with 2 frailty conditions, and 16.0% (95% CI, -16.3% to 39.4%) for those with 3 or more frailty conditions. (Included frailty conditions were vision or hearing loss; impaired mobility; difficulty toileting, bathing, dressing, grooming, or going out; skin, urinary, or gastrointestinal problems; resting tremor; changes in sleep; and hypertension.)

Another potentially serious adverse effect of vaccination can occur in persons with egg allergies. Only the recombinant, trivalent, standard-dose influenza vaccine (Flublok [RIV3]); recombinant, quadrivalent, standard-dose, inactivated influenza vaccine (Flublok Quadrivalent [RIV4]); and the recombinant, quadrivalent, standard-dose inactivated influenza vaccine produced in cell culture (Flucelvax

Quadrivalent [RIV4]) are manufactured without the use of eggs as incubators. The recombinant, quadrivalent, standard-dose inactivated influenza vaccine produced in cell culture (Flucelvax Quadrivalent) uses starter cultures grown in eggs, meaning there is a theoretical 5×10^{-8} mcg of total egg protein per 0.5-mL vaccine dose.²⁷

Influenza Vaccination Recommendations for 2017-2018

The position of the ACIP is that any age-appropriate IIV formulation (standard-dose or high-dose, trivalent or quadrivalent, unadjuvanted or adjuvanted) or RIV is acceptable for persons 65 years or older. The ACIP states quite clearly, "No preferential recommendation is made for any specific vaccine product."²⁷ Instead, ACIP specifies only that all eligible patients should be vaccinated in a timely manner and that patients should not wait to vaccinate if a specific product is not available. The difficulty in recommending one product over another in the 65 years or older group lies in the lack of data: Most data are for the 18- to 64-year age group. Currently, no head-to-head data exist that compare the high-dose with the adjuvanted vaccines in patients 65 years or older. The ACIP recommends²⁷:

- Persons with a history of egg allergy who have experienced only urticaria (hives) after exposure to egg should receive influenza vaccine. Any licensed and recommended influenza vaccine may be used
- Persons who report having had reactions to egg involving symptoms other than urticaria (hives), such as angioedema, respiratory distress, lightheadedness, or recurrent emesis, or who required epinephrine or another emergency medical intervention, may receive an influenza vaccination. Any licensed and recommended influenza vaccine may be used. Vaccine administration should be supervised by a healthcare provider who is able to recognize and manage severe allergic conditions
- A previous severe allergic reaction to influenza vaccine is a contraindication to future receipt of the vaccine, regardless of the component suspected of being responsible for the reaction

Conclusions

Vaccination is a proven tool to reduce the morbidity and mortality associated with seasonal influenza, especially in the elderly population. The ACIP recommends that most people receive the vaccine, but particularly at-risk populations, including elderly persons and those who work with at-risk populations. New vaccine preparations have been introduced to boost vaccine seroprotection in older patients. They contain higher doses of antigen, vaccine adjuvants, or recombinant proteins. Healthcare systems will be challenged to integrate these new agents into full use. Factors affecting use depend heavily on the cost-effectiveness of the vaccines. As we

will see in the next article, use of these vaccines by managed care organizations will require superior vaccine effectiveness and improved cost-effectiveness, as compared with currently available trivalent, standard-dose influenza vaccines. ■

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