Seasonal influenza vaccination in adults

INTRODUCTION — Influenza is an acute respiratory illness caused by influenza A or B viruses. It occurs in epidemics nearly every year, mainly during the winter season in temperate climates. Influenza viruses change their antigenic characteristics frequently, and their subsequent spread depends upon the susceptibility of the population to viruses with novel antigens. Annual influenza vaccination is an important public health measure for preventing influenza infection [1-4]. The protection provided by influenza vaccines is based upon induction of virus-neutralizing antibodies, mainly against the viral hemagglutinin.

The role of influenza vaccination in the prevention of seasonal influenza will be reviewed here. The use of influenza vaccine in immunocompromised hosts, pregnant women, patients with chronic liver disease, patients with end-stage renal disease, healthcare workers, and travelers is discussed separately. (See associated topic reviews.)

The clinical manifestations and diagnosis of influenza in adults, the role of antiviral agents for the prevention and treatment of seasonal influenza, and vaccines against the 2009 pandemic H1N1 influenza ("swine influenza") virus, H5N1 avian influenza, and H7N9 avian influenza are also reviewed elsewhere. Seasonal influenza vaccination in children is also presented separately. (See "Clinical manifestations of seasonal influenza in adults" and "Diagnosis of seasonal influenza in adults" and "Prevention of seasonal influenza with antiviral drugs in adults" and "Treatment of seasonal influenza in adults" and "Treatment and prevention of pandemic H1N1 influenza ('swine influenza')", section on 'Vaccination' and "Avian influenza vaccines" and "Avian influenza A H7N9: Treatment and prevention", section on 'Vaccine development' and "Seasonal influenza in children: Prevention with vaccines".)

OVERVIEW

Influenza activity — The United States Centers for Disease Control and Prevention (CDC), in collaboration with the World Health Organization (WHO) and its reporting network, tracks influenza virus isolates throughout the world to monitor disease activity and to predict the appropriate components for the annual influenza vaccine. Surveillance information, which is updated weekly during influenza season, is available on the CDC website. In addition, FluNet, a database for global influenza virus surveillance, is

available on the WHO website. The typical seasonal trends of influenza activity in the United States are shown in the following Figure (figure 1).

Indications — In 2010, the United States Advisory Committee on Immunization Practices (ACIP) expanded the recommendation for influenza vaccination to include all individuals six months of age and older [5]. This represented a change from previous guidelines, which recommended influenza vaccination for individuals at increased risk of influenza complications and close contacts of such individuals. High-risk individuals, their close contacts, and healthcare workers should remain high-priority recipients in vaccination campaigns (table 1). (See 'High-priority groups' below.)

Older adults and individuals with underlying health problems are at increased risk for complications of influenza, including death. Influenza vaccination not only reduces the risk of influenza infection but also reduces the severity of illness in those who are infected [6,7]. Influenza virus usually causes an acute self-limited febrile illness in healthy young adults; vaccination results in fewer influenza infections and fewer missed days from work in such individuals [8].

Widespread immunization of children has appeared to result in herd immunity, with a reduction in influenza infections in unvaccinated children and adults of all ages. (See "Seasonal influenza in children: Prevention with vaccines", section on 'Herd immunity'.)

Antigenic composition — Influenza virus is remarkable for its high rate of mutation, compromising the ability of the immune system to protect against new variants [9]. As a consequence, new vaccines are produced each year to match circulating viruses. Currently, vaccine production takes, on average, six months from the selection of seed strains to the final vaccine product. The decision of which influenza antigens to include in the vaccines is made in advance of the influenza season and is based upon global surveillance of influenza viruses circulating at the end of the prior influenza season [10]. As a result, rarely there are mismatches between the vaccine strain and the circulating strain that result in reduced efficacy of the vaccine.

Current influenza vaccines are trivalent or quadrivalent (table 2) [4]. The trivalent vaccine contains two influenza A virus antigens and one influenza B virus antigen, whereas the quadrivalent vaccine contains two influenza A antigens and two influenza B antigens.

The WHO recommends that influenza vaccines for use during the 2015 to 2016 influenza season in the northern hemisphere (November to April) contain the following strains [11,12]:

- A/California/7/2009 (H1N1)-like virus (against 2009 pandemic H1N1 influenza)
- A/Switzerland/9715293/2013 (H3N2)-like virus
- B/Phuket/3073/2013-like virus
- B/Brisbane/60/2008-like virus (included in the quadrivalent vaccines only)

Two of the vaccine antigens are different from those used in the 2014 seasonal influenza vaccine in the southern hemisphere and the 2014 to 2015 seasonal influenza vaccines in the northern hemisphere.

The WHO recommends that influenza vaccines for the 2016 influenza season in the southern hemisphere (May to October) contain the following strains [13]:

- A/California/7/2009 (H1N1)-like virus (against 2009 pandemic H1N1 influenza)
- A/Hong Hong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like virus
- B/Phuket/3073/2013-like virus (included in the quadrivalent vaccines only)

The influenza A H3N2 and influenza B vaccine antigens for trivalent vaccines are different from those used in the 2015 influenza vaccines for the southern hemisphere and the 2015-2016 influenza vaccines for the northern hemisphere.

Influenza A viruses, in particular, undergo periodic changes in the antigenic characteristics of their envelope glycoproteins, the hemagglutinin and the neuraminidase [14]. Among the large number of influenza A viruses that infect mammals, three major subtypes of hemagglutinins (H1, H2, and H3) and two subtypes of neuraminidases (N1 and N2) have commonly caused disease in humans; other subtypes have caused sporadic infections (eg, H5N1, H7N9). Major changes in these glycoproteins are referred to

as antigenic shifts, and minor changes are called antigenic drifts. Antigenic shifts are generally associated with pandemics of influenza A. Antigenic drifts are associated with the usual annual epidemics and necessitate annual updating of the vaccine antigen makeup. (See "Epidemiology of influenza", section on 'Antigenic shifts' and "Epidemiology of influenza", section on 'Antigenic drifts'.)

Influenza B viruses have a lesser propensity for antigenic changes, and only antigenic drifts in the hemagglutinin have been described. More subtypes of hemagglutinins and neuraminidases can exist in avian influenza A viruses compared with the influenza A viruses that cause seasonal influenza infections. (See "Epidemiology, transmission, and pathogenesis of avian influenza", section on 'Background'.)

Two genetic lineages of influenza B viruses have circulated since the mid-1980s. The potential benefit of using a quadrivalent vaccine is illustrated by a report showing that during 12 seasonal influenza outbreaks between 1999 and 2012, 42 percent of all influenza B infections were caused by viruses of the genetic lineage that was not included in the trivalent vaccine used during those seasons [15]. Influenza B viruses accounted for 26 percent of all typed viruses.

The current vaccination strategy is vulnerable to the emergence of epidemic or pandemic strains that are not represented in the current vaccine. Ongoing research is focused on developing a universal vaccine that would elicit protective antibodies directed against conserved viral proteins. (See 'Immunogenicity, efficacy, and safety' below and 'Universal vaccines' below.)

Vaccine formulations — In the United States, two different types of influenza vaccine are available, inactivated influenza vaccines (IIVs) and a live-attenuated vaccine (LAIV) (table 3 and table 2) [2,4]. The choice of which influenza vaccine to administer to individual patients is discussed below. (See 'Choice of vaccine formulation' below.)

Available FDA-approved vaccines include [4]:

- **Standard-dose trivalent and quadrivalent inactivated influenza vaccines** – The available inactivated influenza vaccines in the United States are preparations of split virion or subunit vaccines that have been inactivated. The standard-dose inactivated influenza vaccines are approved by the FDA for intramuscular injection in adults of any age. These vaccines are

produced in embryonated chicken eggs. During the 2015 to 2016 influenza season, both quadrivalent and trivalent formulations of inactivated vaccines are available. (See 'Antigenic composition' above.)

In 2014, the FDA approved the intramuscular administration of a formulation of trivalent inactivated influenza vaccine (Afluria) using a jet injector device (PharmaJet Stratis needle-free injection system) for adults between 18 and 64 years of age [16].

●**Standard-dose quadrivalent LAIV** – The intranasally administered live-attenuated influenza vaccine (FluMist) is approved for healthy nonpregnant adults up to 49 years of age. This vaccine uses a master attenuated cold-adapted donor virus from which reassortants are generated that have hemagglutinin and neuraminidase antigens from strains that were circulating at the time that the annual vaccine was designed. The vaccine is produced in embryonated chicken eggs. Starting in the 2013 to 2014 influenza season, only a quadrivalent formulation of LAIV is available; during previous seasons, LAIV was a trivalent vaccine.

●**High-dose trivalent** inactivated influenza vaccine — An intramuscular high-dose inactivated influenza vaccine (Fluzone high-dose) is approved for individuals ≥65 years of age; the vaccine contains 60 mcg of each vaccine antigen instead of 15 mcg, which is the standard dose [17]. (See 'High-dose vaccine' below.)

●**Adjuvanted trivalent inactivated influenza vaccine** — In November 2015, an adjuvanted trivalent inactivated influenza vaccine (Fluad) was approved for use in individuals ≥65 years of age [18]. It is the first adjuvanted seasonal influenza vaccine to be approved in the United States. It is expected to be available in the winter or spring of 2016. (See 'Adjuvanted vaccine' below.)

●**Intradermal low-dose quadrivalent** inactivated influenza vaccine — An intradermal formulation of the inactivated influenza vaccine (Fluzone intradermal) is approved for individuals between 18 and 64 years of age [19]. This vaccine uses one-fifth of the usual amount of vaccine antigens and is delivered using an ultra-fine needle that is 1.5 mm in length [20]. It is supplied in a single-dose, preservative-free syringe. In late 2014, a quadrivalent

formulation was approved by the FDA [21]. The quadrivalent formulation is expected to be available for the 2015 to 2016 influenza season and will replace the trivalent formulation. (See 'Intradermal delivery' below.)

●**Trivalent** inactivated influenza vaccine **produced in cultured cells** — A trivalent inactivated influenza vaccine produced in cultured mammalian cells (Flucelvax) is approved for individuals ≥18 years of age [22,23]. (See 'Cell-based inactivated vaccine' below and 'Alternative production methods' below.)

●**Trivalent** inactivated influenza vaccine **produced using recombinant DNA technology and a baculovirus expression system** — A trivalent recombinant hemagglutinin influenza vaccine (Flublok), which is produced using recombinant DNA technology and a baculovirus expression system that produces virus-like particles, is approved for individuals 18 years of age or older [24,25]. Unlike all of the other formulations, which contain both hemagglutinin and neuraminidase antigens, the recombinant vaccine contains only hemagglutinin antigens. (See 'Recombinant hemagglutinin vaccine' below and 'Alternative production methods' below.)

Choice of vaccine formulation — The choice of vaccine formulation depends upon several factors, including age, comorbidities, pregnancy, and risk of adverse reactions (table 3) [2,4]:

●**For healthy nonpregnant adults up to 49 years of age**, we prefer either a quadrivalent inactivated vaccine or LAIV (which is also quadrivalent) when possible. In contrast, the ACIP has not stated a preference for the quadrivalent vaccine over the trivalent vaccine.

●**For all individuals ≥50 years of age and for individuals with a contraindication to receiving LAIV** (eg, immunocompromise; chronic cardiovascular, pulmonary, or metabolic disease; pregnancy; severe allergy to an influenza vaccine or its components), we recommend an inactivated influenza vaccine. We favor a quadrivalent formulation over a trivalent formulation when possible. (See 'Contraindications and precautions' below.)

●**Individuals between 18 and 64 years of age** can receive an intradermal formulation of the quadrivalent inactivated influenza vaccine (Fluzone intradermal). This vaccine can be used as an alternative to other inactivated vaccines, but the ACIP has not stated a preference for this

vaccine over the standard inactivated vaccines. Patients who are needle phobic and have a contraindication to LAIV may prefer the intradermal vaccine over an intramuscular vaccine because the intradermal vaccine is delivered using a short ultra-fine needle. A drawback to the intradermal inactivated influenza vaccine is that it has been associated with higher rates of injection site reactions (erythema, induration, swelling, and pruritus, but not pain) than the intramuscular inactivated influenza vaccines. (See 'Intradermal delivery' below and 'Inactivated vaccines' below.)

An alternative for needle-phobic adults between 18 and 64 years of age is the intramuscular administration of a trivalent inactivated influenza vaccine (Afluria) using a jet injector device (PharmaJet Stratis needle-free injection system). Use of the needle-free injection system was approved by the FDA in August 2014. Similar to the intradermal formulation, the needle-free injection system is associated with a higher frequency of local injection site reactions than the use of needle and syringe. (See 'Needle-free jet injector' below and 'Inactivated vaccines' below.)

●**For individuals ≥65 years of age**, we suggest the intramuscular high-dose trivalent inactivated influenza vaccine (Fluzone high-dose) when available rather than a standard-dose inactivated vaccine, particularly in those taking a statin. It should be noted that the ACIP has not stated a preference for this vaccine over the standard-dose inactivated influenza vaccine in older adults. Mild to moderate local reactions are more common with the high-dose vaccine than with standard-dose vaccine, but the incidence of serious adverse events is similar. (See 'High-dose vaccine' below and 'Efficacy' below.)

●Inactivated influenza vaccines do **not** appear to exacerbate chronic neurologic diseases, such as multiple sclerosis, and can therefore be given to individuals with such conditions [26,27].

●Recommendations for **individuals with egg allergy** are presented separately. As noted above, two vaccine formulations that are not produced in eggs are available (Flublok and Flucelvax). Flublok contains no ovalbumin, whereas Flucelvax may contain trace amounts of

ovalbumin because the vaccine seed strain used to make this vaccine is passaged in eggs. (See "Influenza vaccination in individuals with egg allergy" and 'Vaccine formulations' above.)

Vaccine supply — In some influenza seasons, supply of the inactivated vaccine has been limited or delayed. A possible way to increase the supply of the inactivated vaccine is to administer lower doses via either the intramuscular or the intradermal route. This approach is discussed below. (See 'Reduced-dose vaccines' below and 'Intradermal delivery' below.)

Schedule — Outbreaks of influenza generally occur during the winter months in the northern and southern hemispheres (which occur at different times of the year). A single dose of an influenza vaccine should be administered to adults annually and offered soon after the vaccine becomes available, ideally by October in the northern hemisphere and May in the southern hemisphere [2,4]. The timing of vaccination should balance maximizing the likelihood that vaccine-induced protection will persist throughout the influenza season (which is of particular concern in older and immunocompromised individuals) with avoiding missed opportunities to vaccinate or vaccinating after influenza viruses have begun circulating [4]. (See 'Waning of antibodies and effectiveness' below.)

Vaccination should continue to be administered throughout the influenza season, the length of which varies from year to year. Evidence of significant influenza activity in the community should be used to determine how late in the season vaccination should be offered. (See 'Influenza activity' above.)

Travelers to tropical regions should be reminded that influenza occurs throughout the year in the tropics [28]. In addition, summertime outbreaks of influenza have occurred on cruise ships in the northern and southern hemispheres and during pandemics, such as the 2009 H1N1 influenza A pandemic. Repeat vaccination is not necessary in those who received routine vaccination at the appropriate time in the previous fall or winter. (See "Immunizations for travel", section on 'Influenza vaccine'.)

Inactivated influenza vaccines can be given to individuals with minor respiratory illnesses with or without fever [29]. We avoid the use of LAIV in patients with upper respiratory tract infections because of concern that local factors (eg, interferon production, nasal congestion) might prevent adequate influenza virus replication and exposure to influenza antigens. Influenza vaccination should be delayed until symptoms

have resolved in patients with moderate or severe acute illness, with or without fever, to avoid confusion between the underlying illness and adverse effects of the vaccine.

Administration with other vaccines — Inactivated influenza vaccines do not interfere with the immune response to other inactivated vaccines or to live virus vaccines [2,30]. An inactivated influenza vaccine may therefore be administered at the same time, but at a different site, as other recommended vaccines. The deltoid muscle is the preferred site for intramuscular administration in adults [4].

LAIV can also be administered at the same time as other live virus vaccines or inactivated vaccines [31]. However, if it is not administered on the same day as other live virus vaccines (eg, zoster vaccine), it should be administered at least four weeks later because the immune response to one live virus vaccine might be impaired if administered within four weeks of another live virus vaccine.

High-priority groups — Although annual influenza vaccination is recommended for all individuals ≥6 months of age, when the vaccine supply is limited, those who are at increased risk for complications and household contacts and caregivers of such persons should be the highest priority recipients (table 1) [2]. (See 'Indications' above.)

Individuals who are at increased risk for influenza complications include those at the extremes of age, pregnant women, immunocompromised hosts, those with certain chronic diseases, and others; the groups at high risk for influenza complications are presented in the following Table (table 4) [2]. Although there are no data regarding the risk for severe or complicated influenza among asplenic individuals, influenza is a risk factor for secondary bacterial pneumonia, which can be severe in such patients. (See "Clinical manifestations of seasonal influenza in adults", section on 'Secondary bacterial pneumonia'.)

Pregnancy — Based upon evidence that influenza infection is associated with excess complications and death in pregnant women, the ACIP recommends the inactivated influenza vaccination for pregnant women, regardless of the stage of pregnancy, and of women who might be pregnant during the influenza season [2]. Influenza vaccination in pregnant women is discussed in detail separately. (See "Immunizations during pregnancy", section on 'Inactivated influenza vaccine'.)

Immunocompromised hosts — The ACIP recommends the inactivated influenza vaccine for immunocompromised patients, including HIV-infected individuals, patients with cancer, and transplant recipients [2]. LAIV is contraindicated in immunocompromised individuals. Influenza vaccination in the setting of immunocompromise is discussed in detail separately. (See 'Choice of vaccine formulation' above and "Immunizations in HIV-infected patients", section on 'Influenza vaccine' and "Immunizations in patients with cancer", section on 'Influenza vaccine' and "Immunizations in solid organ transplant candidates and recipients", section on 'Influenza' and "Immunizations in hematopoietic cell transplant candidates and recipients", section on 'Influenza'.)

Healthcare workers and household contacts — Vaccination is particularly important for individuals who might transmit influenza to persons at high risk for complications; such individuals include healthcare workers, workers at chronic healthcare facilities, providers of home care to persons at high risk, and household contacts of persons in high-risk groups (table 1) [2].

Healthcare workers and household contacts who have close contact with severely immunocompromised persons who require a protective environment should receive an inactivated influenza vaccine rather than the live-attenuated influenza vaccine; if LAIV is given, the healthcare worker or household contact should avoid contact with severely immunocompromised patients for seven days after receipt [4,32]. LAIV may be given to other healthcare providers.

Vaccination of healthcare workers is discussed in greater detail separately. (See "Immunizations for healthcare providers", section on 'Influenza vaccine'.)

Need for annual vaccination — Annual immunization is necessary even if the previous year's vaccine contained one or more of the antigens to be administered because immunity declines during the year following vaccination [2,4,33]. Annual vaccination reduces mortality from influenza by 41 percent (95% CI 13 to 60 percent) [34]. Among those who had been vaccinated previously, mortality was reduced by 75 percent (95% CI 31 to 91 percent), but, among those being vaccinated for the first time, the reduction in mortality was only 9 percent (95% CI 0 to 59 percent).

Annual vaccination is also associated with a reduction in mortality in older adults who have been vaccinated previously (hazard ratio 0.76, 95% CI 0.70-0.83) but not in those who received the vaccine for the first time [35]. (See 'Effect on mortality' below.)

Waning of immunity and effectiveness in older individuals is discussed in greater detail below. (See 'Waning of antibodies and effectiveness' below.)

IMMUNOGENICITY, EFFICACY, AND SAFETY — Because influenza vaccines produced in eggs take approximately six months to manufacture, they necessarily contain antigens from strains that circulated during the previous year. The protective efficacy of the vaccine is largely determined by the relationship (closeness of "fit" or "match") between the strains in the vaccine and viruses that circulate in the outbreak. A study that compared the effectiveness of the inactivated influenza vaccine during influenza seasons with differing degrees of vaccine match illustrates the importance of the fit between circulating influenza virus strains and the vaccine [36]. During the 2004 to 2005 influenza season, the antigenic match was only 5 percent compared with 91 percent during the 2006 to 2007 season, which resulted in a vaccine effectiveness of 10 versus 52 percent, respectively. During the 2014 to 2015 influenza season in the United States, influenza A H3N2 viruses predominated and more than half of these viruses contained H3N2 antigen that was antigenically different (drifted) from that included in that season's influenza vaccines [37]. The adjusted overall vaccine effectiveness for the 2014 to 2015 influenza season was 23 percent [38].

A repeated finding in various studies is that vaccination produces a greater reduction in serologically confirmed influenza than in clinical influenza. Universal influenza vaccination in Ontario, Canada, has also been shown to reduce the number of antibiotic prescriptions during periods of peak influenza activity [39].

Healthy adults — A number of studies have evaluated the efficacy or immunogenicity of various influenza vaccines in different populations.

Trivalent inactivated vaccines — Although many studies evaluating the efficacy of influenza vaccines in healthy adults have been published and efficacy is often estimated to be between 70 and 90 percent, a

2012 comprehensive review suggested that efficacy may be considerably lower [40]. In a 2012 meta-analysis (performed by the same group that did the comprehensive review) that included eight randomized trials of the inactivated influenza vaccines in adults aged 18 to 64 years over nine influenza seasons, vaccine efficacy for preventing laboratory-confirmed influenza was 59 percent (95% CI 51 to 67 percent) [41]. Of note, higher rates of efficacy and effectiveness have been reported in trials that used serologic endpoints; such trials were excluded from this meta-analysis because using serologic endpoints is likely to lead to an overestimation of benefit.

In a 2014 meta-analysis of randomized trials and observational studies of healthy adults, the overall efficacy of inactivated vaccines in preventing laboratory-confirmed influenza was 60 percent (53 to 66 percent), corresponding to a number needed to vaccinate (NNV) of 71 [27]. The overall effectiveness of inactivated vaccine against influenza-like illness was 16 percent (95% CI 5 to 25 percent), corresponding to a NNV of 40 [27]. The difference between these two results relates to the different incidence of these endpoints among the study populations; 2.4 percent of unvaccinated individuals versus 1.1 percent of vaccinated individuals developed laboratory-confirmed influenza, whereas 15.6 percent of unvaccinated individuals versus 9.9 percent of vaccinated individuals developed an influenza-like illness, respectively. The discrepancy between protection against laboratory-confirmed influenza and influenza-like illness is likely related to the well-known lack of protection offered by influenza vaccines against non-influenza respiratory viruses.

The match between the antigens included in the influenza vaccines and circulating influenza strains would be expected to have an important influence on the efficacy of the vaccines. In the 2014 meta-analysis described above, inactivated vaccines were 16 percent effective (95% CI 9 to 23 percent) in preventing influenza-like illness when strains contained in the vaccine antigenically matched circulating strains [27]. On the other hand, inactivated vaccines were not protective against influenza-like illness when the degree of matching between the vaccine and circulating influenza strains was absent or unknown. In contrast, the efficacy of inactivated vaccines for preventing laboratory-confirmed influenza was similar when the match was good and when the match was absent or unknown (62 versus 55 percent, respectively).

Several studies have shown that influenza vaccination is less effective in individuals who were vaccinated during the current and previous season(s) compared with individuals who were vaccinated during the current season only [42-45]. The reasons for this remain to be elucidated. Nevertheless, annual vaccination continues to be recommended because annual vaccination is required to protect against newly circulating influenza strains included in the current year's vaccine and because vaccinating the population is likely to provide benefit even if the vaccine has reduced efficacy in those who are vaccinated annually. In an analysis of a hypothetical cohort, over a two-year period, the highest number of cases will occur in the population that remains unvaccinated; a single vaccination is better than no vaccination, and vaccination in both years is likely to prevent more disease than vaccination in a single year [46]. (See 'Need for annual vaccination' above.)

Because inactivated influenza vaccines are thought to provide nonsterilizing immunity, influenza vaccination might have a greater effect on reducing illness severity than on preventing infection [47]. In a case-control study in which hospitalized patients with laboratory-confirmed influenza infection were matched against outpatients with laboratory-confirmed influenza and outpatient controls, vaccine effectiveness was 75 percent for preventing outpatient influenza cases, 60 percent for preventing influenza-associated hospitalizations, and 89 percent for preventing severe influenza [6]. Among hospitalized patients with influenza, those who had been vaccinated against influenza were less likely to have severe influenza than those who had not been vaccinated (adjusted odds ratio [aOR] 0.42, 95% CI 0.22-0.80).

Influenza vaccination also appears to reduce the risk of influenza pneumonia. In a multicenter case-control study of adults and children hospitalized for community-acquired pneumonia (CAP) during three influenza seasons, those with laboratory-confirmed influenza-associated pneumonia had lower odds of having received an influenza vaccine during the same influenza season compared with those with CAP not associated with influenza (aOR 0.43; 95% CI 0.28-0.68) [48]. The estimated vaccine effectiveness for preventing influenza-associated pneumonia was 57 percent (95% CI 32 to 73 percent).

A case-control study in adults 40 years or older found that influenza vaccination was associated with a reduction in the rate of first acute myocardial infarction (aOR 0.81, 95% CI 0.77-0.85) [49].

Cell-based inactivated vaccine — In 2012, the US Food and Drug Administration (FDA) approved a trivalent inactivated influenza vaccine produced in cultured mammalian cells (Flucelvax) for individuals ≥18 years of age [22,23]. In a placebo-controlled trial that included 7728 adults, the efficacy of Flucelvax was 84 percent [22,23], which is comparable to standard available influenza vaccines. In addition, in seven trials that included 6281 adults, rates of serious events in patients who received cell-based vaccine groups were similar to those who received egg-based vaccine or placebo [23]. Several other randomized trials have demonstrated that the immunogenicity and efficacy of influenza vaccines produced using mammalian cell lines are comparable to vaccines produced using embryonated eggs [7,50-53].

As noted above, vaccines that are not produced in eggs are particularly useful for patients with egg allergies. Because the vaccine seed strain used to make Flucelvax is passaged in eggs, traces of ovalbumin may be present [4]. (See 'Choice of vaccine formulation' above and "Influenza vaccination in individuals with egg allergy".)

Other benefits of cell-based vaccines (eg, faster production time) are discussed below. (See 'Alternative production methods' below.)

Recombinant hemagglutinin vaccine — The FDA has approved a second egg-free trivalent recombinant hemagglutinin influenza vaccine (Flublok), which is produced using recombinant DNA technology and a baculovirus expression system that produces virus-like particles, for individuals 18 years of age or older [24,25]. This vaccine was shown to be safe and immunogenic in a randomized trial that included 460 adults [54]. In a randomized trial that included 4648 adults, Flublok was approximately 45 percent effective against all circulating influenza strains, despite substantial antigenic mismatch between the vaccine antigens and circulating viruses; 96 percent of influenza viruses isolated from trial participants contained antigens that differed from the vaccine antigens [55]. Adverse events were similar to those that occur with conventional egg-based inactivated influenza vaccines [24].

Live-attenuated vaccine — A randomized trial compared the live-attenuated influenza vaccine (LAIV) preparation with placebo in 4561 healthy, employed adults followed through an influenza season [8].

Vaccination was associated with significant reductions in severe febrile illnesses (19 percent), febrile upper respiratory tract illnesses (24 percent), and days of work lost for febrile upper respiratory tract illnesses (28 percent). The vaccine was well tolerated and appeared to protect against the prevailing strain of influenza A that season, despite the virus showing considerable drift from the vaccine strain.

In a 2014 meta-analysis of randomized trials and observational studies in healthy adults, LAIV had an overall effectiveness of 10 percent for preventing influenza-like illness, corresponding to a number needed to vaccinate (NNV) of 46 [27]. Overall efficacy for preventing laboratory-confirmed influenza was 53 percent, corresponding to a NNV of 39.

Comparisons of inactivated and live-attenuated vaccines — Although in children LAIV appears to be more effective than the inactivated vaccine, studies in adults have shown that the inactivated vaccine is either equivalent to or more effective than the live-attenuated vaccine [56-60]. (See "Seasonal influenza in children: Prevention with vaccines", section on 'LAIV compared with IIV'.)

Comparisons of inactivated and live-attenuated vaccines have shown the following:

- A randomized trial compared the intramuscular inactivated vaccine and LAIV in 5210 healthy individuals over five years of age [56]. For preventing culture-positive influenza A infection, the inactivated and live-attenuated vaccines were 76 and 85 percent effective against H1N1 influenza and 74 and 58 percent effective against H3N2 influenza, respectively. The differences between the two vaccines were not statistically significant.
- A randomized trial compared the inactivated vaccine to LAIV in 1247 healthy adults during the 2004 to 2005 influenza season [57]. Both vaccines had similar efficacy against culture-proven influenza A infection (74 percent), despite the fact that most circulating viruses were dissimilar to those included in the vaccines. In contrast, the inactivated vaccine was superior to LAIV against culture-confirmed type B influenza infections (80 versus 40 percent efficacy).
- In another randomized trial that included 1952 adults vaccinated during the 2007 to 2008 influenza season, the inactivated vaccine was superior to LAIV against influenza infection as detected by viral culture, real-time polymerase chain reaction, or both (68 versus 36 percent

absolute efficacy) [58]. During the same influenza season, 90 percent of isolates were influenza A H3N2 and 9 percent of isolates were influenza B. The absolute efficacy against the influenza A strain was 72 percent for the inactivated vaccine compared with 29 percent for LAIV.

- In a large surveillance study of United States military personnel during three influenza seasons between 2004 and 2007, immunization with the inactivated vaccine was associated with lower rates of healthcare visits for pneumonia and influenza compared with the LAIV (8.6 versus 19.4 per 1000 person-years in 2004 to 2005; 7.8 versus 10.9 per 1000 person-years in 2005 to 2006; and 8.0 versus 11.7 per 1000 person-years in 2006 to 2007) [59]. However, among individuals who had not been immunized the previous year, the effect of LAIV was comparable to the inactivated vaccine during the 2005 to 2006 and 2006 to 2007 seasons. Whether these results can be generalized to other populations is uncertain.

Intradermal delivery — Alternate methods of vaccine administration have been developed in an attempt to improve immunogenicity, particularly in older adults in whom the immune response may be attenuated. Intradermal administration should theoretically be more effective than intramuscular delivery because of stimulation of dendritic cells, which are specialized antigen-presenting cells. Another potential benefit is that patients who are needle phobic may prefer the intradermal vaccine, since it is delivered using a short ultra-fine needle than the other inactivated influenza vaccines. The intradermal vaccine has been evaluated in several studies, with varying results:

- In an open-label trial, 119 adults were randomly assigned to a conventional intramuscular injection or 40 percent of the usual dose (6 versus 15 mcg of hemagglutinin per strain) administered intradermally [61]. In comparison with the full-dose intramuscular injections, intradermal injections of the reduced dose resulted in similar antibody responses among persons 18 to 60 years of age but not among those over the age of 60 years.
- A similar study evaluated the immunogenicity of a conventional intramuscular injection or 20 percent of the usual dose (3 mcg of hemagglutinin per strain) administered intradermally in

healthy adults between the ages of 18 and 40 [62]. The rates of seroprotection were high and similar in the two groups (84 to 100 percent for the different strains).

- In a trial that included adults 65 years or older, there were no differences in immunogenicity between reduced-dose (60 percent) intradermal administration and intramuscular administration at the reduced or full dose [63].
- In a trial of adults over age 60, those who received the inactivated influenza vaccine using an intradermal microinjection system had higher antibody titers, seroprotection rates, and seroconversion rates compared with those who were vaccinated using routine intramuscular administration of the same dose [64].

Adverse effects are discussed below. (See 'Inactivated vaccines' below.)

Needle-free jet injector — Needle-free vaccine technology is available for immunizing needle-phobic patients and reducing the risk of needlestick injuries to healthcare workers. An example of needle-free technology is the jet injector, a device that uses a high-pressure narrow jet of liquid vaccine to penetrate tissue [65]. In a noninferiority trial, 1250 healthy adults between the ages of 18 and 64 years were randomly assigned to receive one dose of a trivalent inactivated influenza vaccine given either intramuscularly with a needle-free jet injector or with needle and syringe. The immune response to influenza vaccine given with the jet injector device was comparable to the immune response to influenza vaccine given with needle and syringe.

Adverse reactions are discussed below. (See 'Inactivated vaccines' below.)

Older adults — More than 90 percent of seasonal influenza-related deaths occur among people over 60 years of age [66], and older adult patients also have increased morbidity from the disease.

Standard-dose inactivated vaccines

Efficacy — The efficacy of the inactivated influenza vaccine in older adult patients (in whom LAIV is not recommended) has been evaluated in a few randomized trials [67-69] and multiple observational studies, both in the community and in long-term care facilities [70-79], as well as in sicker patients such as those with chronic lung disease [80-82], with conflicting results.

In a 2010 Cochrane meta-analysis of three randomized trials of inactivated influenza vaccines in older individuals, the vaccines were 58 percent effective against influenza (95% CI 34 to 73 percent) [83]. Based on a meta-analysis of two randomized trials, the vaccines were 43 percent efficacious against influenza-like illness (95% CI 21 to 58 percent). Both the authors of the Cochrane review and the authors of a 2012 systematic review concluded that there are inadequate high-quality data from randomized trials and observational studies to assess the efficacy of influenza vaccines in individuals ≥65 years of age [41,83].

A 2008 case-control study evaluated 1173 cases and 2346 controls among community-dwelling older individuals during three pre-influenza periods and influenza seasons, periods when there was good antigenic match between the influenza vaccine and circulating viruses [76]. This study found that influenza vaccination did not reduce the risk of pneumonia (including those who did not require hospitalization), after adjusting for the presence and severity of comorbidities. In contrast, in a 2012 cohort study of community-dwelling older individuals that evaluated 12.6 million person-influenza seasons, vaccination was associated with a reduction in the composite endpoint of hospitalization (for pneumonia and influenza) and death during influenza season (aOR 0.86, 95% CI 0.79-0.92) [84]. In another study of older individuals, vaccination was 58 percent effective at preventing medically attending laboratory-confirmed influenza illness in adults ≥50 years of age as well as in adults ≥65 years of age [85].

Even when vaccine efficacy is low, vaccination is likely to prevent hospitalizations in the older adult population. In a modeling study, during the 2012 to 2013 influenza season (a moderate to severe season), among individuals ≥65 years of age in the United States, a vaccine with 10 percent effectiveness and 66 percent coverage would have averted approximately 13,000 hospitalizations and a vaccine with 40 percent effectiveness would have averted approximately 60,000 hospitalizations [86].

Since protection against influenza is suboptimal in older adults, it is not surprising that the outbreaks of influenza have occurred in nursing homes where 80 to 98 percent of residents were vaccinated [75]. (See 'Healthcare workers' below.)

Statins are used commonly in older adults with hyperlipidemia and are known to have immunomodulatory effects, which could affect vaccine responses. In an observational study conducted in the context of a randomized trial that evaluated influenza vaccines in individuals >65 years of age, hemagglutination inhibition (HAI) geometric mean titers to various influenza strains were 38 to 67 percent lower in those receiving chronic statin therapy than in those not receiving it [87]. In addition, in a large retrospective cohort study conducted over nine influenza seasons in the United States, statin use was associated with reduced influenza vaccine effectiveness against medically attended acute respiratory illness [88]. In an adjusted analysis, influenza vaccine effectiveness against medically attended acute respiratory illness was lower among statin users than statin non-users during periods of local (14.1 versus 22.9 percent; mean difference 11.4 percent, 95% CI -1.7 to 26.1 percent) and widespread (12.6 versus 26.2 percent; mean difference 18.4 percent, 95% CI 2.9 to 36.2 percent) influenza virus circulation. The observed associations between statin use and vaccine effectiveness could be due to confounding, as patients who are being treated with statins are likely to be at differing baseline risk of influenza from those not treated with statins. Although these studies raise the possibility that older patients receiving statins are less likely to be protected by the influenza vaccine than those not receiving statins, such individuals should still receive statins, when indicated, as well as an influenza vaccine (preferably the high-dose vaccine) annually. Further study is necessary to evaluate the impact of statins on influenza vaccine effectiveness against laboratory-confirmed influenza [88]. (See 'Choice of vaccine formulation' above.)

Effect on mortality — It has been difficult to demonstrate an improvement in survival after influenza vaccination in older adult patients in randomized trials because mortality is a rare endpoint. Some studies have observed a significant reduction in death from influenza or pneumonia [83], but some experts have suggested that frailty selection bias in cohort studies has led to an overestimation of any mortality benefit of influenza vaccination in older adults [89]. The following studies illustrate the range of findings and some of the limitations in study design:

- A pooled cohort study demonstrated a small but significant reduction in mortality in vaccinated older individuals (1.0 versus 1.6 percent in unvaccinated individuals) [71]. A sensitivity analysis was performed to detect unmeasured confounders. Even when a higher

rate of confounders was assumed, there was still a significant reduction in mortality. Other studies have supported this finding [90].

●The difficulty of using observational data to evaluate the effect of influenza vaccine on mortality is illustrated by a prospective case-control study of patients (mostly over the age of 65) with CAP. The study assessed the impact of influenza vaccination on in-hospital mortality in patients admitted during the off-season for influenza [91]. A significant mortality reduction was observed in vaccinated patients (odds ratio [OR] 0.49, 95% CI 0.30-0.79). However, when adjustments were made to address confounding factors (eg, functional and socioeconomic status), the mortality benefit became nonsignificant (aOR 0.81, 95% CI 0.35-1.85). This study shows that the presence of bias may overestimate the mortality benefit of influenza vaccination [92].

●A large cohort study of community-dwelling older individuals did not detect a mortality benefit from influenza vaccination [84]. An important limitation of this study was the likely underreporting of vaccination status, which could have contributed to the vaccine appearing ineffective [93].

●Annual revaccination has been associated with a reduction in mortality in older adults. A report from the Netherlands of over 26,000 community-dwelling older individuals evaluated the association between the number of consecutive annual influenza vaccinations and all-cause mortality [35]. After adjustment for age, sex, and comorbidities, the following findings were noted:

- •A first vaccination was associated with a nonsignificant annual reduction in mortality risk of 10 percent, while revaccination was associated with a significant 24 percent reduction in mortality overall and a 28 percent reduction during epidemics. There was also a trend toward further benefit with each consecutive vaccination.
- •Vaccination interruption was associated with a strong and significant increase in mortality risk (adjusted hazard ratio 1.25, 95% CI 1.10-1.42), an effect that was reversed with restarting annual vaccination.

Waning of antibodies and effectiveness — There has been concern that the response to annual vaccination might attenuate over time, particularly in older individuals. However, a 2008 literature review that included studies of individuals >60 years old found that, after influenza vaccination, seroprotection was maintained for at least four months (and often for longer) in all eight studies that assessed antibody responses to the H3N2 component and in five of seven studies that assessed responses to the H1N1 and B components [94]. Following successful immunization, seroprotection rates of 70 to 100 percent were maintained not just at four months (two studies) but also at five months (two studies) and at >6 months (four studies) for the H3N2 and H1N1 influenza A vaccine components. Seroprotection rates were less consistent for the influenza B vaccine component. Both studies that failed the criteria for seroprotection at four or more months following immunization for the H1N1 influenza A and influenza B components also reported failed seroprotection at one month following immunization. This suggests that patients who did not have seroprotective antibodies at four months failed to mount an adequate immune response following vaccination (as opposed to having developed seroprotective antibodies following vaccination that subsequently waned).

A subsequent study showed a decline in antibody titers six months after vaccination in individuals ≥65 years of age, although the titers still met the levels considered adequate for protection [95]. Low prevaccination HAI titer (<1:40) and advanced age were associated with early decline of HAI titers, falling below presumed seroprotective levels around six months following vaccination.

A case-control study showed a decline in vaccine effectiveness with time, particularly in those ≥65 years of age [96]. Vaccine effectiveness (VE) in preventing laboratory-confirmed influenza infection was 61 percent (95% CI 5 to 84 percent) during the first 100 days after vaccination, 42 percent (95% CI -39 to 75 percent) between 100 and 119 days, and zero thereafter.

High-dose vaccine — In 2009, the FDA approved a high-dose trivalent inactivated influenza vaccine, Fluzone high-dose, for individuals ≥65 years of age [17]. (See 'Choice of vaccine formulation' above.)

The FDA approval was based on a trial that compared Fluzone high-dose (60 mcg of hemagglutinin per strain) with standard-dose Fluzone (15 mcg of hemagglutinin per strain) in adults ≥65 years of age that

reported improved rates of seroconversion and an increase in mean HAI titers one month following vaccination in individuals who received the high-dose vaccine [97]. Another randomized trial that compared antibody responses to the high-dose and standard-dose vaccines during the 2011 to 2012 and 2012 to 2013 influenza seasons showed that the high-dose vaccine elicited superior geometric mean titers (except for noninferior titers to influenza A H1N1 in 2012 to 2013) in frail older adult residents of long-term care facilities [98]. Mild to moderate local reactions were more common in those who received the high-dose vaccine [97].

In a subsequent multicenter trial that included 31,989 adults ≥65 years of age, Fluzone high-dose was modestly more effective than standard-dose Fluzone [99]. In the intention-to-treat analysis, 228 individuals in the high-dose group (1.4 percent) and 301 in the standard-dose group (1.9 percent) had laboratory-confirmed influenza associated with an influenza-like illness (relative efficacy 24.2 percent, 95% CI 9.7 to 36.5 percent). After vaccination, HAI titers and seroprotection rates (the percentage of participants with HAI titers ≥1:40) were higher in the high-dose group. At least one serious adverse event was reported in 8.3 percent of individuals who received the high-dose vaccine compared with 9.0 percent of those who received the standard-dose vaccine. Three recipients of the high-dose vaccine had serious adverse events classified as related to vaccination (cranial nerve VI palsy starting one day after vaccination; hypovolemic shock associated with diarrhea starting one day after vaccination; acute disseminated encephalomyelitis starting 117 days after vaccination); all three events resolved before study completion. No serious adverse events in recipients of the standard-dose vaccine were considered to be related to vaccination. Continued postmarketing surveillance will be necessary to detect potential rare but serious adverse events. The incidence of mild to moderate local reactions was not reported.

In a large retrospective cohort study of United States Medicare beneficiaries ≥65 years of age, receipt of the high-dose vaccine was associated with reduced rates of probable influenza infection and hospital admission for influenza compared with standard-dose vaccine [100]. In contrast, in another large retrospective cohort study of community-dwelling veterans ≥65 years of age in the United States, the high-dose vaccine was not more effective than standard-dose vaccine in protecting against hospitalization for influenza or pneumonia except in those ≥85 years of age [101].

The high-dose influenza vaccine is more expensive than the standard-dose vaccine. However, in a cost analysis of data from the trial in individuals ≥65 years of age that found that the high-dose vaccine was effective [99], the high-dose influenza vaccine appeared likely to result in cost savings compared with the standard-dose vaccine [102].

The immunogenicity of the high-dose vaccine in HIV-infected individuals is discussed separately. (See "Immunizations in HIV-infected patients", section on 'Efficacy, immunogenicity, and safety'.)

Intradermal delivery — Studies of intradermal delivery of influenza vaccines are discussed above, including studies that included older adults. However, the intradermal formulation has only been approved for individuals between the ages of 18 and 64 years. (See 'Intradermal delivery' above and 'Vaccine formulations' above and 'Choice of vaccine formulation' above.)

Adjuvanted vaccine — Adjuvants are substances that amplify the immune response to an antigen [103]. In 2015, the first adjuvanted trivalent influenza vaccine (Fluad) was approved by the US Food and Drug Administration for use in individuals ≥65 years of age [18]. The adjuvanted vaccine was first approved in Italy in 1997 and is currently approved in >35 countries. The vaccine is formulated with the adjuvant MF59, an oil-in-water emulsion of squalene oil.

In a trial that compared the adjuvanted vaccine with an unadjuvanted trivalent inactivated influenza vaccine in 7082 individuals ≥65 years of age, antibody levels were comparable in both groups [18]. However, other studies have shown that MF59-adjuvanted influenza vaccines are more immunogenic than unadjuvanted influenza vaccines [104-106].

No safety concerns were identified among 27,000 individuals [18]. The most common adverse effects were injection site pain and tenderness, myalgias, headache, and fatigue.

Subunit versus split-virion vaccines — Subunit and split-virion vaccines are two different types of inactivated influenza vaccines. Subunit vaccines are purified to remove the internal subviral core. Split-virion vaccines do not undergo this purification step and contain more protein and are more reactogenic than subunit vaccines. In a study of individuals ≥50 years of age, split-virion vaccine

effectiveness was 78 percent and subvirion vaccine effectiveness was 44 percent [107]. Additional studies are needed to confirm these findings.

Dual influenza and pneumococcal vaccination — Although there are no randomized trials that have studied the effects of both vaccines administered together, a cohort study has suggested that dual influenza and pneumococcal vaccination is superior to either vaccine alone for preventing complications in older adults with chronic illnesses [108]. In adults ≥65 years of age with chronic illnesses, dual vaccination with the inactivated influenza vaccine and the pneumococcal polysaccharide vaccine resulted in lower rates of death (hazard ratio [HR] 0.65, 95% CI 0.55-0.77), pneumonia (HR 0.57, 95% CI 0.51-0.64), ischemic stroke (HR 0.67, 95% CI 0.54-0.83), and acute myocardial infarction (HR 0.52, 95% CI 0.38-0.71) compared with unvaccinated individuals. Dual vaccination also resulted in fewer coronary (HR 0.59, 95% CI, 0.44-0.79) and intensive care unit admissions (HR 0.45, 95% CI 0.22-0.94) compared with unvaccinated individuals.

Pneumococcal vaccination is discussed in detail separately. (See "Pneumococcal vaccination in adults".)

Contacts — Vaccination of a population may also be undertaken to protect their contacts. The underpinning for this approach is the concept of "herd immunity," whereby the benefits of immunization may be passed indirectly to vulnerable populations by vaccinating those who may serve as vehicles for disease transmission.

Household contacts — The best data on the effect of influenza vaccination on household contacts come from studies in children, which are discussed in detail elsewhere. (See "Seasonal influenza in children: Prevention with vaccines", section on 'Herd immunity'.)

Some of the key findings are described below:

- LAIV was given to 47 percent of students compared with no intervention in demographically similar elementary schools in four states [109]. The primary objective of the study was to assess the effect of a school-based vaccination program on the households of children attending the schools. During a predicted week of peak influenza activity, all households with children in intervention and control schools were surveyed regarding influenza-like illness

during the previous seven days. There were modest but significant reductions in the numbers of symptoms of respiratory illness and visits to clinicians among adults and children in the intervention households compared with control households. Absenteeism from elementary school and the number of workdays missed by adults were also significantly reduced.

●Inactivated vaccine was administered to offspring of military personnel attending daycare centers [110]. Unvaccinated household contacts of vaccinated children had 42 percent fewer febrile respiratory illnesses than unvaccinated household contacts of unvaccinated children; the degree of protection was greater (80 percent reduction) among school-aged household contacts who also had a 70 percent reduction in school days missed.

Healthcare workers — The efficacy of influenza vaccination in healthcare workers is discussed separately. (See "Immunizations for healthcare providers", section on 'Influenza vaccine'.)

Cost-effectiveness — Several studies have evaluated the cost-effectiveness of influenza vaccine in adults, including older adults [111-115].

●In a large study of healthy adults during two consecutive influenza seasons, the estimated net societal cost compared with no vaccination was $11.17 per person when the vaccine and predominant circulating viruses were well matched compared with $65.59 when the vaccine virus differed from the predominant circulating viruses [111].

●Since vaccine efficacy varies from year to year, another analysis incorporated ten years of influenza surveillance data from the World Health Organization in an attempt to determine cost-effectiveness of vaccine in healthy adults compared to treatment or no intervention [114]. On average, the cost-effectiveness of vaccination compared favorably with other commonly accepted interventions.

●A cost-benefit has also been demonstrated in high-risk older adult patients [115]. Although there was a small net cost for vaccinating older adult patients not at high risk, it was thought that indirect benefits, such as prevention of suffering and lost wages, would compensate for the cost.

ADVERSE REACTIONS

Inactivated vaccines — The inactivated influenza vaccines are generally well tolerated, with the most common side effect being arm soreness at the injection site (in 64 percent of vaccine recipients) [116]. In clinical trials, serious adverse events have been reported rarely. A slightly increased risk of Guillain-Barré syndrome has been associated with the inactivated influenza vaccine during certain influenza seasons, but this added risk appears to be substantially less than the overall health risk posed by naturally occurring influenza. This topic is discussed in greater detail separately. (See "Pathogenesis of Guillain-Barré syndrome", section on 'Influenza vaccination'.)

Immediate IgE-mediated hypersensitivity reactions have been reported rarely following influenza vaccination [2]. Oculorespiratory syndrome, an acute self-limited reaction, was first described during the 2000 to 2001 influenza season in Canada and has been reported occasionally within 24 hours of administration of the inactivated influenza vaccine [2,117]. It is typically mild and is characterized by bilateral conjunctivitis, facial edema, and/or respiratory symptoms (eg, cough, wheezing). It is not thought to be IgE-mediated, and a causal link to influenza vaccination has not been established. However, after changes to the manufacturing process to the vaccine formulation associated with oculorespiratory syndrome, the incidence dropped substantially.

Mild to moderate local reactions are more common with the **high-dose** inactivated influenza vaccine (Fluzone high-dose) than the standard-dose vaccine [97]. During the first year of postmarketing surveillance of the high-dose vaccine, a greater proportion of gastrointestinal complaints (especially vomiting) was reported to the Vaccine Adverse Event Reporting System (VAERS) among recipients of the high-dose vaccine than among recipients of the standard-dose vaccine [118].

The **intradermal** inactivated influenza vaccine has been associated with higher rates of injection site reactions (erythema, induration, swelling, and pruritus, but not pain) than the intramuscular inactivated influenza vaccines [2,119,120].

Needle-free intramuscular administration — of a trivalent inactivated influenza vaccine (Afluria) with a jet injector device is associated with a higher frequency of local injection site reactions than the use of needle and syringe [65]. These include pain, tenderness, itching, redness, swelling, and bruising.

Intranasal vaccine — The live-attenuated influenza vaccine (LAIV) is generally well tolerated, with the most common side effects in adults being rhinorrhea, nasal congestion, headache, and sore throat [121].

Out of 2.5 million people who received LAIV, the following serious adverse events have been reported to the Vaccine Adverse Event Reporting System: possible anaphylaxis (seven), Guillain-Barré syndrome (two), Bell's palsy (one), and asthma exacerbation among individuals with a history of asthma (eight) [122].

CONTRAINDICATIONS AND PRECAUTIONS — Influenza vaccination is contraindicated in patients who have had a severe allergic reaction (eg, anaphylaxis) to an influenza vaccine or its components [2].

It seems prudent to withhold influenza immunization from individuals who developed Guillain-Barré syndrome within six weeks after a previous influenza immunization [2]. (See "Pathogenesis of Guillain-Barré syndrome", section on 'Influenza vaccination'.)

In addition, the live-attenuated intranasal vaccine (LAIV) should **not** be given to [4]:

- Immunocompromised patients (including those with HIV infection and those with immunosuppression caused by medications)
- Pregnant women
- Adults aged ≥50 years
- Individuals who have taken an influenza antiviral medication within the previous 48 hours

Healthcare workers and household members who have close contact with severely immunocompromised persons who require a protective environment should not receive LAIV or should avoid contact with such patients for seven days after receipt [4,32]. LAIV may be given to other healthcare providers. (See "Immunizations for healthcare providers", section on 'Influenza vaccine'.)

Patients with asthma might be at increased of wheezing after administration of LAIV [4]. The safety of LAIV in individuals with chronic cardiovascular (except isolated hypertension), pulmonary, renal, hepatic, neurologic/neuromuscular, hematologic, or metabolic diseases (eg, diabetes) has not been established. These conditions (including asthma) are considered precautions for the use of LAIV.

Egg allergy is considered by the US Food and Drug Administration and the United States Advisory Committee on Immunization Practices to be a contraindication to LAIV administration [4]. However, data have been published suggesting that LAIV is safe in those with egg allergy. These data and recommendations for individuals with egg allergy are presented separately. (See "Influenza vaccination in individuals with egg allergy".)

INVESTIGATIONAL AND ALTERNATIVE APPROACHES — Important drawbacks of traditional influenza vaccines include the need to design new vaccines each year to match circulating strains and the fact that the production process takes several months when embryonated eggs are used.

Alternative production methods — New influenza vaccines have been developed that do not use embryonated eggs as a vehicle for production. Non-egg–based methods are attractive because they are less laborious, have a shorter production time, and do not depend on a supply of eggs [50,103,123]. Furthermore, vaccines made without eggs can be used in individuals who are allergic to eggs. As noted above, two vaccine formulations not produced in eggs are available (Flucelvax and Flublok). (See 'Vaccine formulations' above.)

Mammalian cell line–based vaccines also preserve the structure of the antibody-combining sites on the hemagglutinin antigen (HA), unlike egg-adapted influenza viruses; the preservation of the HA may result in more robust antibody responses [124]. Cell-based vaccines may also induce broader immune responses, which might provide better protection against variant strains. Mammalian cells are also more permissive of influenza virus replication; certain influenza viruses, such as avian H5N1 viruses, do not replicate well in eggs.

There has also been interest in a modified vaccinia Ankara (MVA) vector-based influenza vaccine because it induces an influenza virus-specific T cell response. In a small study, an MVA vector-based

vaccine was safe and immunogenic in healthy individuals and appeared to reduce the incidence of influenza infection following an intranasal challenge compared with unvaccinated individuals [125]. Among vaccinees who developed influenza infection, influenza symptoms were less pronounced and the duration of viral shedding was shorter than in unvaccinated individuals.

Additional vaccines that are being evaluated employ other viral vectors (eg, vaccinia virus, adenoviruses, vesicular stomatitis virus) or utilize virus-like particles [103]. A vaccine that uses recombinant DNA technology and a baculovirus expression system to produce virus-like particles (Flublok) has been approved by the US Food and Drug Administration (FDA). (See 'Recombinant hemagglutinin vaccine' above.)

Universal vaccines — Ongoing research is focused on developing a universal vaccine that would elicit protective antibodies directed against conserved viral proteins [103,126-133]. Such a vaccine would provide protection against drifting influenza strains, as well as against newly emerging pandemic strains [103]. In addition, a universal vaccine might also decrease the emergence of viral escape mutants [126]. Promising targets include the highly conserved external domain of the influenza matrix 2 protein and conserved epitopes from the influenza nucleoprotein, matrix 1 protein, and hemagglutinin protein [103].

Although most influenza vaccines have been designed to elicit a humoral immune response, in a phase I clinical trial, a modified vaccinia virus Ankara vector that encodes the influenza nucleoprotein and matrix 1 protein boosted T cell responses, particularly CD8+ T cell responses, to all influenza A subtypes in healthy adults [134]. Such a vaccine has the benefit of being directed at epitopes within the conserved internal proteins of influenza viruses rather than at the highly variable surface proteins [135].

Most neutralizing antibody responses in individuals who were infected with the H1N1 influenza A strain that caused the 2009 to 2010 pandemic were broadly cross-reactive against epitopes in the hemagglutinin stalk and head domain of multiple influenza strains, suggesting that a universal influenza vaccine might be developed using such immunogens [136].

Reduced-dose vaccines — Vaccine shortages have occurred in some seasons. One approach to address this involves giving a reduced dose of vaccine in order to expand the available supply. In a trial

of half- versus full-dose trivalent inactivated influenza vaccine among healthy individuals who had previously been vaccinated, both doses led to equivalent protective hemagglutination titers (≥1:40) [137]. However, geometric mean titers (GMTs) were slightly lower for all vaccine strains among those who received the reduced dose. Among women 18 to 49 years of age who received the half-dose vaccine, titers were equal or higher than in men who received the full-dose vaccine. Some subjects 50 to 64 years of age who received the half-dose vaccine had GMTs that were unacceptably low. These findings suggest that, in the presence of a vaccine shortage, administering half-dose vaccine to targeted individuals (healthy women between the ages of 18 to 49 who have been vaccinated in previous years) might be an effective strategy.

Using a reduced dose of vaccine by the intradermal route has also been evaluated in several studies, as discussed above. (See 'Intradermal delivery' above.)

RESOURCES

- Vaccine information statement for inactivated and recombinant influenza vaccines from the United States Centers for Disease Control and Prevention (CDC)
- Vaccine information statement for the live-attenuated influenza vaccine from the CDC
- Influenza vaccine availability tracking system from the National Adult and Influenza Immunization Summit

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient information: Flu vaccine (The Basics)" and "Patient information: Flu (The Basics)" and "Patient information: Vaccines (The Basics)" and "Patient information: Vaccines for adults (The Basics)" and "Patient information: Vaccines and pregnancy (The Basics)")
- Beyond the Basics topics (see "Patient information: Influenza prevention (Beyond the Basics)" and "Patient information: Influenza symptoms and treatment (Beyond the Basics)" and "Patient information: Vaccination during pregnancy (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Influenza is an acute respiratory illness caused by influenza A or B viruses. It occurs in epidemics nearly every year, mainly during the winter season in temperate climates (figure 1). Influenza virus is remarkable for its high rate of mutation; this viral evolution compromises the ability of the immune system to protect against new viral variants. As a consequence, new vaccines are produced each year to match the vaccine with the new circulating viruses. The protective efficacy of the vaccine is largely determined by the relationship (closeness of "fit" or "match") between the strains in the vaccine and viruses that circulate in the outbreak. Annual influenza vaccination is an important public health measure for preventing influenza infection. (See 'Introduction' above and 'Antigenic composition' above and 'Immunogenicity, efficacy, and safety' above.)
- Several influenza vaccines are licensed for use in the United States, including inactivated vaccines, which are administered intramuscularly or intradermally, and a live-attenuated vaccine, which is administered intranasally (table 3 and table 2). Current influenza vaccines are trivalent or quadrivalent. The protection provided by influenza vaccines is based upon induction of virus-neutralizing antibodies, mainly directed against the viral hemagglutinin. (See 'Introduction' above and 'Vaccine formulations' above.)

●The United States Advisory Committee on Immunization Practices (ACIP) recommends influenza vaccination for all individuals six months of age and older. High-risk individuals, their close contacts, and healthcare workers should remain high-priority populations in vaccination campaigns (table 1). (See 'Schedule' above.)

●For healthy nonpregnant adults <65 years of age, we recommend annual influenza vaccination (**Grade 1A**) For individuals ≥65 years of age and for other individuals at increased risk for severe influenza (eg, immunocompromise; chronic cardiovascular, pulmonary, or metabolic disease; pregnancy) (table 4), we recommend annual influenza vaccination (**Grade 1B**). (See 'Indications' above.)

●A single dose of an influenza vaccine should be offered soon after the vaccine becomes available, ideally by October in the northern hemisphere and May in the southern hemisphere. Annual immunization is necessary even if the previous year's vaccine contained one or more of the antigens to be administered because immunity declines during the year following vaccination. (See 'Schedule' above and 'Need for annual vaccination' above.)

●The choice of vaccine formulation depends upon several factors, including age, comorbidities, pregnancy, and risk of adverse reactions (table 3 and table 2). For healthy nonpregnant adults up to 49 years of age, we use either an inactivated vaccine or the live-attenuated influenza vaccine (LAIV); in randomized trials of adults, the inactivated vaccine was either equivalent to or more effective than the live-attenuated vaccine. We use an inactivated influenza vaccine in those patients in whom safety and/or efficacy of LAIV has not been established, including adults ≥50 years of age; individuals who are immunocompromised or have chronic cardiovascular, pulmonary, or metabolic disease; pregnant women; and those with egg allergy. We favor a quadrivalent formulation over a trivalent formulation when possible. For individuals ≥65 years of age, we suggest the high-dose inactivated influenza vaccine (Fluzone high-dose) when available rather than a standard-dose inactivated influenza vaccine because the high-dose vaccine is more immunogenic and appears more effective than the standard-dose vaccine in such patients (**Grade 2B**). If possible, individuals on statins should receive the

high-dose vaccine, since statins may impair vaccine responses. Additional guidance regarding the most appropriate formulation for a given patient is provided above. (See 'Vaccine formulations' above and 'Choice of vaccine formulation' above.)

●Recommendations for individuals with egg allergy are presented separately. (See "Influenza vaccination in individuals with egg allergy".)