CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Influenza Vaccination

John J. Treanor, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 75-year-old man who has well-controlled hypertension and mild chronic obstructive pulmonary disease, but who is otherwise healthy, visits his physician in the early fall. He has questions about vaccination against influenza. He asks specifically whether he should receive a standard-dose four-component vaccine or the recently licensed high-dose vaccine, which has only three components. What would you advise, and how strong is the evidence that a vaccine will reduce his risk of influenza?

From the University of Rochester Medical Center, Rochester, NY. Address reprint requests to Dr. Treanor at the Infectious Diseases Division, Department of Medicine, University of Rochester Medical Center, 601 Elmwood Ave., Rochester, NY 14642, or at john_treanor@urmc.rochester.edu.

N Engl J Med 2016;375:1261-8.
DOI: 10.1056/NEJMcp1512870

An audio version of this article is available at NEJM.org

THE CLINICAL PROBLEM

Influenza is a viral infection that is associated with seasonal outbreaks of respiratory illness during the winter months in regions with temperate climates and during rainy seasons in tropical regions. The reasons for seasonal epidemics of influenza are not definitely known. They probably involve a combination of environmental factors such as low humidity and low temperature and social behaviors that facilitate person-to-person transmission of influenza A and B viruses, such as attendance at school and indoor crowding during inclement weather.

At unpredictable intervals, influenza pandemics occur with very high attack rates and severe disease. These pandemics are associated with the emergence of influenza A viruses that, on their surfaces, have hemagglutinin (HA) and neuraminidase (NA) molecules of subtypes that are not currently circulating in human populations. Because of a lack of prior immunity, humans can be highly susceptible to infection and disease from these subtypes. Influenza A viruses with a wide variety of HA and NA subtypes are enzootic in waterfowl, swine, and other animals, which are the probable source of these new viruses.

Influenza in otherwise healthy persons is characterized predominantly by fever, myalgias, cough and other respiratory symptoms, and malaise. In most persons, recovery from these symptoms occurs in 5 to 7 days, but even in healthy persons symptoms of fatigue and malaise may not completely resolve for several weeks. Influenza may cause more severe pulmonary symptoms through direct invasion of the lung (leading to primary viral pneumonia) or by altering lung defense mechanisms in a variety of ways that lead to bacterial superinfection. This superinfection, which may occur simultaneously with influenza or follow it by days to weeks, may be responsible for much of the disease burden associated with influenza. Other potential complications of influenza include myositis and myocarditis, toxic shock syndrome related to *Staphylococcus aureus* superinfection, and various complications in the central nervous system.

KEY CLINICAL POINTS

INFLUENZA VACCINATION

- Influenza is responsible for a considerable burden of hospitalizations and deaths, and the negative effects of this infection are greatest in young children and older adults.
- The ability of influenza vaccines to prevent disease varies from year to year depending on the match between the vaccine and circulating viruses; the effectiveness of these vaccines is monitored by networks in the United States and elsewhere.
- Although the protection afforded by vaccination is incomplete, vaccines have repeatedly been shown to confer considerable protection against influenza and are recommended for all children and adults.
- Some studies have suggested that repeated vaccinations may be associated with reduced vaccine effectiveness, but annual vaccinations are still recommended.
- The Advisory Committee on Immunization Practices (ACIP) has not recommended any one specific influenza vaccine over others. However, because of troubling results of recent effectiveness studies, the ACIP is recommending that live attenuated influenza vaccine not be used during the 2016–2017 season in the United States.

The effects of influenza traditionally have been assessed by comparing hospitalizations and deaths during an influenza season with a baseline model. These calculations suggest that seasonal influenza epidemics in the United States are responsible for between 55,000 and 431,000 hospitalizations due to pneumonia and influenza each year and as many as 49,000 deaths.[1] Investigators in more recent studies that link hospitalization data with laboratory confirmation of influenza and adjust for variations in testing have reached similar conclusions.[2,3]

The magnitude of the disease effect of seasonal influenza varies depending both on the degree to which the current seasonal virus is different from previous viruses and on the specific predominating subtype. The highest levels of influenza-attributable hospitalizations and deaths tend to occur in years in which H3N2 viruses predominate.

Factors associated with increased risks of severe influenza and complications of influenza include an age of 5 years or younger or of 65 years or older and the presence of chronic medical conditions, including cardiac or pulmonary disease, diabetes, neuromuscular conditions that affect respiration, and immunosuppressive conditions such as human immunodeficiency virus infection.[4] Obesity[5] and pregnancy[6,7] are also recognized risk factors for serious complications of influenza; however, hypertension alone is not a recognized risk factor for these complications. Severe disease and death due to influenza can occur in persons who do not have known risk factors. Thus, in the United States and several other countries, annual vaccination of all persons is currently recommended.

STRATEGIES AND EVIDENCE

IMMUNITY TO INFLUENZA

Antibodies against the viral attachment protein HA prevent entry of the virus into cells, neutralize virus in vitro, and are associated with protection in clinical studies. The serum HA-inhibition (HAI) assay is the primary means of assessing serum antibody responses to standard influenza vaccines. Higher levels of HAI antibodies are associated with increased protection against influenza, but no absolute value of antibodies uniformly predicts protection.

Multiple other immune mechanisms also contribute to protection against influenza. These mechanisms include mucosal immunity, antibodies to NA, cellular immunity in the form of virus-specific CD4+ or CD8+ T cells, and possibly antibodies to other viral proteins such as the minor envelope protein M2 and the structural nucleoprotein.

INFLUENZA VACCINES

Influenza can be prevented by vaccination,[8] and several influenza vaccines are currently available in the United States[9] (Table 1). The production of an inactivated influenza vaccine (IIV) typically involves growth of influenza viruses in embryonated hens' eggs, followed by concentration of the virions, chemical inactivation and disruption of the envelope, and partial purification of the HA and NA proteins.

Since they were initially licensed in the United States decades ago, numerous refinements have been made in the methods used in manufacturing these vaccines, but the basic strategy for in-

Table 1. Influenza Vaccines Available in the United States.*

Vaccine and Manufacturer (Trade Name)	Description	Components	Dose	Route of Administration	Approved Age
IIV3: inactivated influenza vaccine, trivalent, standard dose					
Seqirus (Afluria)	Inactivated egg-grown virus, partially purified HA and NA	H1, H3, Bv	15 μg HA per component	Intramuscular	≥5 yr†
Seqirus (Fluvirin)	Inactivated egg-grown virus, partially purified HA and NA	H1, H3, Bv	15 μg HA per component	Intramuscular	≥4 yr
IIV4: inactivated influenza vaccine, quadrivalent, standard dose					
GSK (Fluarix)	Inactivated egg-grown virus, partially purified HA and NA	H1, H3, By, Bv	15 μg HA per component	Intramuscular	≥3 yr
ID Biomedical (FluLaval)	Inactivated egg-grown virus, partially purified HA and NA	H1, H3, By, Bv	15 μg HA per component	Intramuscular	≥3 yr
Sanofi Pasteur (Fluzone)	Inactivated egg-grown virus, partially purified HA and NA	H1, H3, By, Bv	15 μg HA percomponent	Intramuscular	≥6 mo‡
IIV4 ID: inactivated influenza vaccine, intradermal					
Sanofi Pasteur (Fluzone intradermal)	Inactivated egg-grown virus, partially purified HA and NA	H1, H3, By, Bv	9 μg HA per component	Intradermal	18–64 yr
IIV3 HD: inactivated influenza vaccine, trivalent, high dose					
Sanofi Pasteur (Fluzone high dose)	Inactivated egg-grown virus, partially purified HA and NA	H1, H3, Bv	60 μg HA per component	Intramuscular	≥65 yr
AIIV3: adjuvanted inactivated influenza vaccine, trivalent					
Seqirus (Fluad)	Inactivated egg-grown virus, partially purified HA and NA, MF59 adjuvanted	H1, H3, By	15 μg HA per component	Intramuscular	≥65 yr
CCIIV4: cell culture–derived inactivated influenza vaccine, quadrivalent					
Seqirus (Flucelvax)	Inactivated cell culture–grown virus, partially purified HA and NA	H1, H3, By, Bv	15 μg HA per component	Intramuscular	≥4 yr
RIV3: recombinant influenza vaccine, trivalent					
Protein Sciences (Flublok)	Recombinant HA protein	H1, H3, Bv	45 μg HA per component	Intramuscular	≥18 yr
LAIV4: live attenuated influenza vaccine, quadrivalent					
AstraZeneca (FluMist)	Egg-grown live attenuated virus	H1, H3, By, Bv	$10^{7.0}$ FFU virus per component	Intranasal	2–49 yr§

* B denotes B/Brisbane/60/2008–like virus, Bv B/Brisbane/60/2008 (Victoria lineage), By B/Florida/4/2006 (Yamagata lineage), FFU fluorescent focus units, HA hemagglutinin, H1 A/California/7/2009 (H1N1)pdm09–like virus, and H3 A/Hong Kong/4801/2014 (H3N2)–like virus.
† Although this vaccine is licensed for use in persons 5 years of age or older, the Advisory Committee on Immunization Practices (ACIP) recommends that administration of this vaccine should be restricted to persons 9 years of age or older because younger children have more frequent febrile reactions to this vaccine.
‡ Children younger than 36 months of age receive one half the standard dose (i.e., 7.5 μg HA per component).
§ The ACIP has recommended against the use of this vaccine in the 2016–2017 season because of apparently decreased effectiveness.

The New England Journal of Medicine

ducing immune responses has remained the same. Since 1977, inactivated vaccines have contained three components — a recent H1N1 virus, an H3N2 virus, and an influenza B virus — in a so-called trivalent formulation (IIV3). Since approximately 1980, two antigenically distinct lineages of influenza B virus have cocirculated,[10] and many inactivated vaccines now include both B lineages in a quadrivalent formulation (IIV4). Studies have shown that the addition of the fourth component does not interfere with the immune response to the other three components, but direct evidence of enhanced protection from IIV4, as compared with IIV3 formulations, is lacking.

Two vaccines that involve the use of alternative substrates for production have also been licensed. One is made in mammalian cell culture (CCIIV4),[11] and the other is composed of recombinant baculovirus-expressed HA proteins produced in insect cells (RIV3).[12] Because these viruses do not need to be adapted to eggs for production, they can potentially be produced more quickly and avoid incorporation of mutations associated with egg adaptation.

One live attenuated influenza vaccine (LAIV4) is licensed in the United States. Production of this vaccine involves gene reassortment to rapidly generate reproducibly attenuated vaccine viruses containing the genes for the HA and NA from the antigenic target virus and all other genes from a well-characterized attenuated master donor virus. LAIV4 is administered intranasally, and the limited replication of the vaccine viruses in the upper respiratory tract induces immunity against influenza.[13] However, the specific immune responses that are responsible for the protective efficacy of LAIV4 have not been clearly identified.

VACCINE PROTECTION

Evaluation of the protection against influenza-related illness conferred by influenza vaccine is complicated by multiple variables, including the population being assessed, the study design, and the end points used, as well as by the particular season and the predominant viruses involved. Three primary methods have been used to assess the protection conferred by influenza vaccine (Fig. 1). Randomized, controlled trials (Fig. 1A) are the reference method for assessing the protective effect, and the estimates they provide are defined as vaccine "efficacy." One meta-analysis of randomized trials of IIV in adults showed a pooled efficacy of 59% (95% confidence interval, 51 to 67) in prevention of laboratory-confirmed influenza,[14] and randomized trials have also established the efficacy of live attenuated influenza vaccine.[13,15] Randomized trials reduce the potential for bias, but a limitation of trials is that they may be performed in selected populations that may not be representative of the target population. In addition, randomized, controlled trials are complex and expensive, and they are not a practical approach to assessing vaccine performance on an annual basis.

Observational cohort studies (Fig. 1B) are also used to assess vaccine protection, and their results are defined as vaccine "effectiveness." One type of effectiveness study involves the use of health care databases or similar population-based data sets to assess outcomes in vaccinated and unvaccinated enrollees.[16] Several such studies have shown substantial reductions in the risks of cardiovascular events[17] and all-cause mortality[18] among vaccinated persons. However, these studies can be limited by confounding factors that differ between vaccinated and unvaccinated persons and that also affect the outcome of interest. For example, persons who choose to be vaccinated may have better health in general and better compliance with other recommendations regarding health than those who do not make this choice. Conversely, persons who are housebound because of debilitating illness may not be vaccinated; thus, there may be an overestimation of the effect of influenza vaccine.[19]

The test-negative case–control approach (Fig. 1C) is intended to minimize biases related to access to health care and to minimize misclassification of influenza cases. Persons who meet a specific case definition of influenza-like illness are tested for the presence of influenza with the use of a highly sensitive and specific test such as reverse-transcriptase polymerase chain reaction, and the vaccination status of those who test positive is compared with that of those who test negative.[20] Networks to establish yearly estimates of vaccine effectiveness with the use of this approach have been established in the United States and in many other countries. Overall estimates of effectiveness in these studies have ranged from 10 to 60%, with lower estimates among older adults and in years in which there is a poor antigenic match.[21]

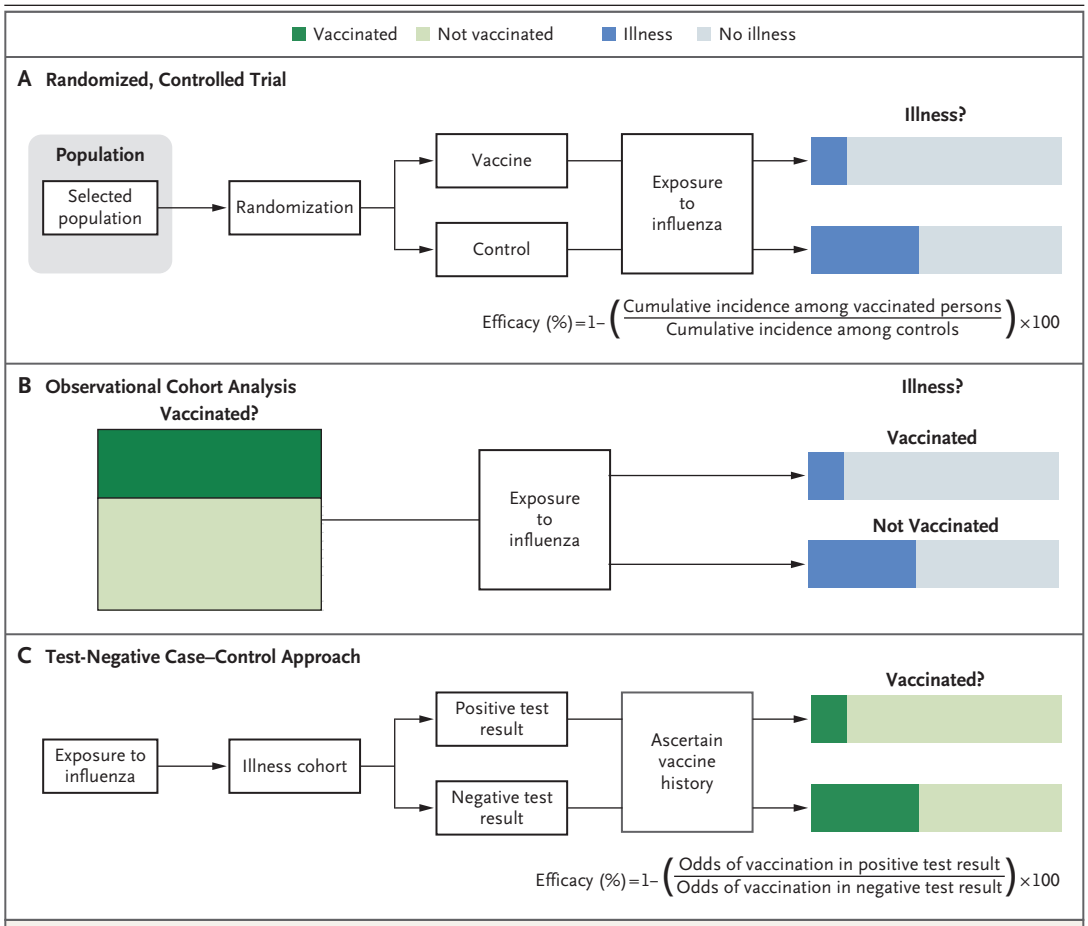

Figure 1. Three Approaches to Determining the Protective Effect of Influenza Vaccine.

As shown in Panel A, in a randomized, controlled trial, persons are selected according to prespecified entry criteria and are randomly assigned to a vaccine group or a control group. Some form of prospective surveillance is then undertaken, and the cumulative incidence of influenza is determined in the two groups. As shown in Panel B, in an analysis of cohorts derived from health care databases, records of visits due to illness and those for vaccination are analyzed and the frequencies of outcomes in vaccinated and unvaccinated persons are compared. As shown in Panel C, in the test-negative case–control design, persons who meet the prespecified definition of illness undergo a highly sensitive and specific test for influenza. The proportions of persons with a history of vaccination among test-positive persons and test-negative controls are compared. The designs shown in Panels B and C involve adjustment for potential confounding variables that may affect rates of both vaccination and illness.

Although these studies consistently show the value of influenza vaccination, they also show that the protection afforded by vaccination is far from complete. Attempts to improve the performance of IIVs have included the use of increased doses and adjuvants. Although the dose–response curve for IIVs is rather flat, administration of increased doses of HA protein does result in levels of postvaccination serum HAI antibodies that are higher than those with lower doses.[22] In one very large, randomized, comparative trial, a vaccine containing approximately four times the standard dose of HA was shown to provide significantly greater protection than the standard-dose vaccine against laboratory-confirmed influenza in persons who were 65 years of age or older (incidence of influenza, 1.9% in the standard-dose group, vs. 1.4% in the high-dose group).[23] The enhanced protective effect was primarily against H3N2 viruses, the subtype with the greatest effect on older adults. Some,[24] but not all,[25] postmarketing studies of this high-dose vaccine (IIV3 HD) have confirmed the enhanced effectiveness of high-dose vaccine in older persons. Serious adverse events have not

been more frequent with the high-dose vaccine than with the standard-dose vaccine,[23] but pain at the injection site has been reported more often (36% vs. 24%).[22]

The addition of immune-enhancing substances, or adjuvants, is another method of improving the performance of influenza vaccine. Oil-in-water–based emulsions have strong antibody-enhancing and dose-sparing effects on pandemic formulations of IIV. Although their effects on the response to seasonal vaccines are not as great overall as their effects on the response to pandemic formulations, adjuvants are associated with increased antibody responses in young children and older adults. Studies of vaccine effectiveness in countries where the oil-in-water–based adjuvant MF59 vaccine is licensed have indicated better effectiveness of this influenza vaccine in older adults than the effectiveness of conventional IIV.[26] The MF59 adjuvanted vaccine (Fluad) was recently approved for use in adults 65 years of age or older in the United States.

AREAS OF UNCERTAINTY

A major challenge related to influenza vaccination is the constant antigenic evolution of the viruses. The immune response to infection or vaccination is focused on the infecting or immunizing virus; viruses with mutations in the key antibody epitopes of the HA and NA can evade these responses and reinfect previously immune persons. Because of this phenomenon, influenza vaccines must be reformulated annually to provide a match between the antigens contained in the vaccine and the circulating viruses to which recipients are likely to be exposed.

The specific influenza viruses that will be included in the vaccine each year are determined by worldwide surveillance and antigenic characterization of human viral isolates by the Global Influenza Surveillance and Response System of the World Health Organization. Currently, the production process requires that these decisions be made in February to allow for the production of vaccines to be distributed in the Northern Hemisphere in the following fall.[27]

Because at least one of the components of the vaccine is changed each year, influenza vaccines are generally administered annually. However, recent analyses have suggested that such repeated annual immunizations may be associated with diminishing effectiveness of the vaccine.[28-32] It has even been suggested that repeated vaccination may largely explain the diminished efficacy of influenza vaccine in older adults.[33] The mechanism underlying this phenomenon is not known, but it has been postulated to involve antigen sequestration by prior antibodies, which decreases presentation to the immune system. Consistent with this theory, some data suggest that the inhibitory effect of prior vaccination is greatest when the vaccine component or components are not different.[34]

Observational studies have recently called into question the effectiveness of LAIV. Analysis of data collected from 2010 through 2014 showed similar levels of effectiveness of LAIV and IIV against H3N2 and B viruses, but a decreased effectiveness of LAIV, especially against H1N1 viruses in the 2010–2011 and 2013–2014 seasons.[35] Preliminary data for 2015–2016 have also suggested minimal effectiveness of LAIV, and the Advisory Committee on Immunization Practices (ACIP) has recommended that LAIV not be used in the 2016–2017 vaccination season. The reason for the apparent decreased effectiveness of LAIV as compared with the efficacy shown in the original studies[13] is unclear, but it could also be related to repeated immunizations and increased baseline immunity, which might interfere with vaccine-virus replication.

There is considerable interest in the development of more broadly cross-protective influenza vaccines that would not require constant updating and annual administration. Most recent efforts have focused on invariant regions of the HA itself as potential targets. Studies of the B-cell response after infection with the pandemic H1N1 virus have revealed that under circumstances in which the immune system is exposed to a new HA, some of the B-cell response is directed against conserved epitopes on the stalk region of the HA.[36,37] Monoclonal antibodies made by these B cells have neutralizing ability in vitro and can protect animals by passive transfer in vivo.[38,39] Other studies have identified stalk-specific antibody responses after seasonal infection or the receipt of various vaccines.[40,41] Efforts are ongoing to develop vaccines that could stimulate vigorous stalk-specific antibody responses[42] and potentially provide protection against multiple HA subtypes that share the

same stalk. Results of studies of such potentially broadly protective vaccines in humans are not yet available.

GUIDELINES

The ACIP[9] provides recommendations for vaccination against influenza in the United States, and similar bodies provide recommendations in other countries. Current recommendations in the United States are for annual immunization of all persons, with a two-dose schedule for children younger than 8 years of age who have not been previously immunized and a single dose for all other persons. The ACIP does not preferentially recommend any specific vaccine in populations for which these vaccines have been licensed, but it has recommended that LAIV not be used during the 2016–2017 season.

CONCLUSIONS AND RECOMMENDATIONS

Existing data on the protective effect of current IIVs do not provide sufficient evidence of superiority of any one formulation over another to definitively support the exclusive use of any specific vaccine in persons such as the man described in the vignette. The availability of a specific vaccine is often the main determining factor.

In discussing options with the man described in the vignette, I would note the moderately enhanced protective efficacy of an IIV3 high-dose vaccine, as compared with standard-dose IIV3 vaccine, as well as the potential advantages of an IIV4 vaccine, which includes both influenza B lineages. Because H3N2 viruses are of the subtype most commonly associated with severe disease in older adults, I might recommend the high-dose vaccine if it is available, pending data from randomized trials comparing the two vaccines. However, the most important strategy is to ensure that he is vaccinated and that the opportunity to provide protection against influenza, imperfect as it might be, is not missed.

Dr. Treanor reports serving without payment on the advisory board for Protein Sciences; receiving fees for serving on advisory boards for Novartis (Seqirus), Merck, and GSK; receiving grant support from Sanofi Pasteur, Novartis (Seqirus), CSL, and Protein Sciences; and holding a pending patent related to mutations to increase attenuation of live attenuated influenza vaccine (US 14/695,544). No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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