

Clinical Practice

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 authors' clinical recommendations.

INFLUENZA VACCINATION FOR HEALTHY YOUNG ADULTS

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A healthy 33-year-old woman who works in an office calls to ask whether she should receive influenza vaccine. How should this patient be advised?

THE CLINICAL PROBLEM

Vaccination against influenza virus is the primary strategy to reduce the morbidity and mortality associated with influenza. Because the benefit of vaccination is greatest for persons at increased risk for severe influenza and its complications as a result of age or underlying medical conditions, members of this group and those in close contact with them have been the focus of recommendations from the Advisory Committee on Immunization Practices (ACIP) and other professional organizations (Table 1). Nonetheless, since studies in the past few years have documented reduced rates of illness and visits to physicians and a decrease in the number of days of sick leave among healthy, working adults who receive the vaccine,² an increasing number of healthy adults who are younger than 65 years of age — and their employers — have been expressing interest in vaccination. Because such people are at low risk for hospitalization or for death from influenza, the magnitude of benefit from vaccination is lower in this group and the small risk associated with vaccination more important.

The strains to be included in the vaccine are selected by the Food and Drug Administration during the first three months of each year. Therefore, the production schedule is tight, and unanticipated problems in production may result in delays in availability.^{3,4}

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Background

Influenza is characterized by the abrupt onset of constitutional and respiratory signs and symptoms such as fever, myalgia, headache, severe malaise, non-productive cough, sore throat, and rhinitis. Frequent antigenic changes in the surface glycoproteins of influenza A and B viruses lead to the development of new strains of the same subtype. In most years, influenza occurs in less than 15 percent of adults.⁵ When influenza virus is known to be present in a community, about two thirds of persons with signs and symptoms of the illness have been found to have influenza on the basis of laboratory tests.⁶

Less than half of all adults with influenza seek medical attention,⁵ and the time lost from work because of an episode of influenza-like illness in otherwise healthy, working adults ranges from 0.8 to 4 days.⁵ Those who care for an adult with influenza-like illness lose an average of 0.4 day of work per episode of illness.⁷ The likelihood that influenza will develop in a household contact of an infected person ranges from 10 percent to 19 percent.^{8,9} Adults who care for children with influenza have higher rates of absenteeism from work, and the rates of illness among household and community contacts of such children are also likely to be higher.¹⁰

The risk of complications of influenza, including hospitalization and death, is much higher among people who are at least 65 years of age and people with underlying medical conditions than among otherwise healthy adults who are younger than 65 years.^{1,11,12} Women who are more than 13 weeks pregnant are at higher risk for hospitalization from cardiorespiratory conditions than nonpregnant women.¹ Influenza epidemics are responsible for more deaths in the United States than is any other vaccine-preventable disease, resulting in an average of approximately 20,000 deaths (more than 90 percent of which are among persons 65 years of age or older) and 114,000 hospitalizations annually.^{1,13}

Rates of Vaccination

Current rates of influenza vaccination fall far short of the Healthy People 2010 national objectives of 90 percent for persons who are at least 65 years of age and 60 percent for younger adults at high risk. In 1999, less than 70 percent of persons who were at least 65 years of age reported having been vaccinated against influenza in the preceding 12 months,¹⁴ and the rate was only 31 percent among adults 18 to 64 years of age who had high-risk conditions.¹ The rates are especially low among pregnant women.¹⁵ In 1999, about one third of the younger adults who were vac-

TABLE 1. TARGET GROUPS FOR INFLUENZA VACCINATION.***Persons at increased risk for complications**

Persons 65 years of age or older
 Residents of nursing homes and other long-term care facilities that house persons of any age who have chronic medical conditions
 Adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma
 Adults and children who have required medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathy, or immunosuppression (including immunosuppression caused by medications or infection with the human immunodeficiency virus)
 Children and teenagers (age, 6 months to 18 years) who are receiving long-term aspirin therapy and therefore might be at risk for Reye's syndrome if they contract influenza
 Women who will be in the second or third trimester of pregnancy during the influenza season

All persons 50 to 64 years of age†**Persons who can transmit influenza to those at high risk**

Physicians, nurses, and other personnel in both hospital and outpatient-care settings, including emergency-response workers
 Employees of nursing homes and long-term care facilities who have contact with residents or patients
 Employees of assisted-living facilities and other residences for persons in groups at high risk
 Persons who provide home care to persons in groups at high risk
 Household members (including children) of persons in groups at high risk

*The groups reflect the recommendations of the Advisory Committee on Immunization Practices.¹

†This group has an increased prevalence of persons with high-risk conditions. Persons 50 to 64 years of age who do not have high-risk conditions also benefit from vaccination through decreased rates of influenza, decreased absenteeism from work, and decreased need for medical visits and medication, including antibiotics.

cinated received the vaccine at a doctor's office and another third received the vaccine at work.¹⁶

Although 70 million to 80 million doses of vaccine have been produced annually in recent years in the United States, about twice as many Americans (152 million) fall within groups for which vaccination is specifically recommended. Since a large proportion of these people do not seek or are not offered vaccination by health care providers, there has traditionally been enough vaccine to make possible the vaccination of anyone who requests it. Last influenza season and this season, production problems resulted in insufficient supply to meet the usual demand in October and November, necessitating additional recommendations to target initial vaccine supplies to those at highest risk and to health care workers.^{3,4}

STRATEGIES AND EVIDENCE**Benefits of Vaccination in Healthy Adults**

When there is a good match between the strains included in the vaccine and the predominant strains in circulation, as was the case in 9 of the 10 most recent influenza seasons, vaccination reduces the incidence of laboratory-confirmed illness among otherwise healthy adults who are younger than 65 years by 70 to 90

percent^{1,5,17} and reduces the rates of visits to physicians, sick leave, and antibiotic use attributable to influenza-like illness by 34 to 44 percent, 32 to 45 percent, and 25 percent, respectively.^{2,18} Because influenza activity can peak anywhere between late December and early March and because antibodies against the virus typically develop in adults within two weeks after vaccination, the optimal time for vaccination is from the beginning of October through the end of November.¹ As long as there is influenza activity, vaccination after this period is likely to be beneficial in most influenza seasons.¹

Cost of Vaccination

Although the influenza vaccine is effective in healthy young people and relatively inexpensive (about \$7), costs associated with vaccination (e.g., the vaccine itself, its administration, medical care for side effects of the vaccine, and time lost from work to receive the vaccine) may not be offset by the savings realized from preventing influenza (e.g., fewer visits to physicians and hospitalizations and less time lost from work). In two randomized studies of healthy, working adults 18 to 64 years of age, the cost of vaccination, from a society-wide perspective, ranged from a net savings of \$47 per person vaccinated to a net cost of \$11 per vaccination, when there was a good match between circulating strains and strains included in the vaccine.^{2,18} Key differences between these studies include a higher rate of illness in the former² and a lower rate of influenza-associated absenteeism from work in the latter.¹⁸ The net cost has been estimated to be \$66 per person in a year with a poor match between circulating strains and strains included in the vaccine.¹⁸ A Monte Carlo simulation model indicates that vaccination of healthy, working adults would result in a net savings of \$14 per vaccination, on average.⁵ Most of the savings in this age group accrue from avoiding losses in productivity, unlike the case among older adults, in whom the main benefit is from reduced medical care costs.

Adverse Effects of Vaccination

The most frequent side effect of vaccination in healthy adults is soreness at the injection site. These local reactions are generally mild and last no more than two days. In one study, 64 percent of vaccine recipients had localized soreness, as compared with 24 percent of placebo recipients.² The rates of systemic effects (e.g., fever, malaise, and myalgia) were similar in the two groups.² Hypersensitivity reactions to residual egg proteins, thimerosal, or other components of the vaccine are rare, but healthy adults who have a history of anaphylaxis in response to these components or to a prior dose of the vaccine should not receive the vaccine. The rates of side effects of split, subunit, and whole-virus influenza vaccines and the immunogenicity of these types are similar among adults.¹

Isolated cases of the Guillain-Barré syndrome were reported with the swine-influenza vaccine of 1976, with an attributable risk of 1 case per 100,000 persons vaccinated.^{19,20} The risk of the development of the Guillain-Barré syndrome as a result of vaccination with current influenza vaccines, if it exists at all, is extremely low and may be outweighed by the risk of severe influenza even among healthy young adults. One study suggested a slight excess risk of one case of the syndrome per million persons vaccinated in the 1992-1993 and the 1993-1994 seasons, but investigations of the influenza season in other years indicated no such association.^{1,21} However, for healthy persons known to have had the Guillain-Barré syndrome within six weeks after a previous influenza vaccination, avoidance of vaccination is prudent, and physicians might consider the use of antiviral chemoprophylaxis as an alternative.¹ Studies of the effect of influenza vaccination in patients with multiple sclerosis have not demonstrated any associated short-term risk of relapse.^{22,23}

One study indicated that the effectiveness of the vaccine waned after the initial vaccination,²⁴ but more recent studies have not supported this finding.²⁵⁻²⁷

Use of Antiviral Drugs

Antiviral drugs are available for the treatment of or prophylaxis against influenza, but they are not a substitute for vaccination.^{1,28} When used for seasonal or postexposure prophylaxis, amantadine and rimantadine are 70 to 90 percent effective in preventing illness from influenza A viruses, whereas the newer drugs zanamivir and oseltamivir are 80 to 90 percent effective in preventing illness due to both influenza A and B viruses; however, zanamivir has not been approved for prophylaxis. Treatment of otherwise healthy adults within 48 hours after the onset of influenza can shorten the duration of the illness by one to one and a half days.²⁸

The side effects of amantadine and rimantadine include anxiety, depression, insomnia, and other central nervous system symptoms, with a respective incidence in otherwise healthy adults of about 10 percent and 2 percent; these drugs cause nausea, vomiting, and dyspepsia in less than 2 percent of subjects.^{1,28} Oseltamivir causes nausea and vomiting in 4 to 6 percent of adults. Zanamivir can occasionally cause bronchospasm or a reduction in airflow and is generally not recommended for patients with underlying airway disease. The average wholesale costs of a five-day course of treatment in adults are \$9.83 for amantadine (or \$1.72 for the generic form), \$18.87 for rimantadine, \$44.40 for zanamivir, and \$53.00 for oseltamivir.²⁸

AREAS OF UNCERTAINTY

The absolute risks of influenza and benefits of vaccination are uncertain for any given influenza season, because of the substantial variation in the timing and severity of annual influenza epidemics. Although the

vaccination of children in day care and of health care workers has been documented to reduce morbidity and mortality among the contacts of these subjects,²⁹⁻³¹ the effect of vaccinating healthy young adults on morbidity and mortality among high-risk or healthy household contacts has not been quantified.

A live attenuated intranasal vaccine has been submitted for licensure, but the effects of this form of vaccine on practice remain to be assessed.^{32,33} This form has been shown to reduce the incidence of severe febrile illness, the number of days of work lost, and the number of health care visits among healthy working adults in a year in which there was a poor match between the strains included in the vaccine and the circulatory strains.³³

GUIDELINES

Guidelines for influenza vaccination have been developed by a number of organizations (Table 2).^{1,34-37} All guidelines recommend the vaccination of high-risk persons and their health care contacts. The ACIP and the American Academy of Family Physicians recommend that healthy adults receive the vaccine if they have a household member with a high-risk condition. The ACIP, the American Academy of Family Physicians, and the American College of Physicians-American Society of Internal Medicine recommend vaccinating all persons 50 to 64 years of age, including those who are healthy. Although none of these organizations actively advocate the vaccination of healthy young adults who do not fall in any of the above groups, none caution against it. Current news on the vaccine supply and the most recent recommendations regarding vaccination, including educational materials for patients and guidelines for implementing patient-reminder systems and other vaccine-delivery strategies, are available at <http://www.cdc.gov/nip/flu>.³⁴

Recent concern about bioterrorism has raised questions about the use of influenza vaccine in healthy persons to reduce the number of cases of "influenza-like illness" that might lead to unnecessary evaluation or treatment. The latest information from the Centers for Disease Control and Prevention regarding this issue is available at the Web site listed above.

CONCLUSIONS AND RECOMMENDATIONS

With respect to the woman in the clinical vignette, the clinician should ask whether anyone she lives with is at increased risk for complications from influenza and whether there has been any recent change in her health status (such as pregnancy) that would put her at increased risk (Table 1). If she does not have a high-risk condition, the physician's advice should depend on the availability of the vaccine, because although the woman stands to benefit personally from vaccination, the highest priority for vaccination should be given to people who are most likely to die from or be hospitalized for influenza.

If an outbreak is caused by a strain of influenzavirus

TABLE 2. GUIDELINES FOR INFLUENZA VACCINATION.*

GROUP	HIGH-RISK PERSONS†	CONTACTS OF HIGH-RISK PERSONS		HEALTHY ADULTS	
		HEALTH CARE PROVIDERS	HOUSEHOLD MEMBERS	50–64 YR OLD	18–49 YR OLD
ACIP	Yes	Yes	Yes	Yes	If requested‡
AAFP	Yes	Yes	Yes	Yes	—
ACP-ASIM	Yes	Yes	—	Yes	—
IDSA	Yes	Yes	—	If requested	If requested
USPSTF	Yes	Yes	—	—	—

*ACIP denotes Advisory Committee on Immunization Practices, AAFP American Academy of Family Physicians, ACP-ASIM American College of Physicians–American Society of Internal Medicine, IDSA Infectious Diseases Society of America, and USPSTF U.S. Preventive Services Task Force.

†High-risk persons are persons who are at least 65 years old and those with certain chronic conditions (the ACIP and AAFP guidelines explicitly include pregnancy in this category).

‡The ability to comply with requests depends on the availability of vaccine. Vaccine can also be administered to children who are at least six months old if their parents request it. Persons who provide essential community services should consider vaccination. Students and other persons in institutional settings should be encouraged to receive the vaccine.

not controlled by the vaccine and the woman lives with someone who is at high risk, prophylaxis with antiviral agents should be considered, regardless of whether she receives the vaccine.

When the supply of vaccine is delayed or limited, health care providers should encourage healthy patients to defer vaccination until higher-risk patients have received the vaccine. Physicians should inform such patients of their low risk of severe complications from influenza and of the fact that later vaccination is still likely to be beneficial. Patients should then be notified when and where the vaccine is available, and health care providers should keep a list of patients who have deferred vaccination and should consider holding special vaccination clinics during evening hours to encourage these patients to return. If the current recommendations have been explained and a low-risk patient still wants to receive the vaccine early, providers should assess their current and expected supply of vaccine and determine the number of high-risk patients who need early vaccination before complying with the request.

When vaccine supplies are sufficient to exceed demand among persons at high risk and their close contacts, vaccination of healthy young adults makes sense, given the very low risk of adverse events and the likelihood that vaccination will provide substantial protection against the disruption of daily life caused by influenza. As long as the vaccine supply remains questionable, well-informed physicians and patients will be in the best position to decide whether to defer vaccination.

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