Influenza remains a major public health concern, resulting in 200,000 hospitalizations and 36,000 deaths every year in the United States. Morbidity and mortality rates are particularly high among older adults. The cornerstone of public health management remains the annual influenza vaccination. In the United States, during the 2011-2012 flu season 64.8% of all persons aged 65 years and older chose to receive the flu shot. That percentage is up significantly from the 1980s, when only 25% of older adults got the flu shot; the 65% figure has remained stable in recent years.
Primary care osteopathic physicians, their allopathic counterparts, pharmacists, nurse practitioners, and physician assistants are on the front lines of informing older adults about the flu shot. Despite voluminous literature and available information, this segment of the population is often confused about many features of the flu shot. They often confuse the “stomach flu” or the common cold for true influenza. Every clinician has heard patients say, “I got the flu shot, but still got the flu.” For this reason, many older patients decide to forgo flu vaccination. Also, confusion exists among persons aged 65 years and older regarding the best time to get the flu shot. Newer types of flu shots are being developed, adding to the choices available to older adults. The purpose of this review is to focus on a few basic principles and issues relating to influenza vaccination in the older population, so that primary care physicians can better counsel those patients. This review also will discuss briefly the evidence for using osteopathic manipulative treatment (OMT) to boost the effectiveness of the influenza vaccine.

Basic principles regarding the influenza virus

The influenza virus is endemic in wild aquatic birds, which means the virus cannot be eliminated from the human population through vaccination and isolation. There will always be an animal population from which a new virus jumps species to infect humans. The virus, which also lives in poultry, only occasionally jumps directly from birds to humans. The more common route is for the virus to jump from birds to swine to humans. Most of the world’s pandemics originate in southern China, simply because this region of the world has a large number of people living in close proximity to large numbers of animals. The influenza virus belongs to the Orthomyxoviridae family, which is divided into 2 genera, with influenza A and influenza B in 1 genus and influenza C in the other. Influenzas A and B are similarly prevalent in the human population, but influenza A has a faster mutation rate and is responsible for pandemics. There are many subtypes of influenza A, distinguished by the antigenic properties of its surface glycoproteins: hemagglutinin and neuraminidase. Influenza C rarely causes illness in humans.

Influenza is caused by a ribonucleic acid (RNA) virus. As occurs with other viruses, the influenza virus reproduces by turning a host cell’s own internal machinery into a replicating factory.

Every clinician has heard patients say, “I got the flu shot, but still got the flu.”

Within 10 hours of entering a human cell, between 100,000 to 1 million copies are ready to break out and infect other cells. Because the viral genetic material is encoded on the simpler and more unstable RNA molecule, the replication process is prone to many errors. These errors are also known as mutations, and mutations render most of the viral copies nonfunctional. Of the 100,000 to 1 million copies, only 1000 to 10,000 will have the capacity to infect other cells. One might think this a weakness of the virus; however, this is 1 of the characteristics that make the influenza virus so difficult to defeat. Many of the functioning copies are slightly different from one another. Rather than labeling these functioning copies as a single viral species, it is more accurate to describe them as a quasi-species, or “mutant swarm.”

The mutant swarm spreads and adapts very quickly, making it difficult for the body’s immune system to counter, thus creating challenges for vaccination. Because the past year’s vaccine may no longer be a good match for a mutant swarm in current circulation, the vaccine is changed from year to year and is given annually. This is 1 reason the effectiveness of the vaccine varies from year to year. When the match is good, the vaccine is more effective; when the match is poor, the vaccine is less effective.

Typically, a current season’s flu vaccine is constructed based on the predominant viruses in common circulation toward the end of the previous season.

Common questions and answers

Answers to general questions regarding influenza are available online at the
Centers for Disease Control and Prevention (CDC), www.cdc.gov/flu. The CDC recommends that everyone aged 6 months and older receive the annual influenza vaccine (Figure). It is stressed that high-risk individuals should be vaccinated, including all persons aged 50 years and older, persons who suffer from chronic disease or who have a weakened immune system, and those with a body mass index of 40 or greater. Likewise, health care providers and those in close contact with high-risk individuals also should be vaccinated. Certainly, if sufficient numbers of persons in a community receive the vaccine, then those who are not vaccinated will be relatively protected through “herd immunity.”

When should people be vaccinated? The CDC recommends vaccinations begin as soon as the manufacturers make the vaccine available, which could be as early as August. This strategy maximizes vaccine coverage in the general population because therapeutic antibody titers generally last for at least 6 months. The influenza season generally starts as early as October and lasts through March. Because it takes 2 to 4 weeks for the body to generate a protective antibody titer, the ideal time for vaccination is at least 2 weeks before the virus shows up in the community, that is, sometime in late September or early October. The CDC does not set a firm date to stop vaccination, because influenza seasons vary in duration and multiple waves of influenza can occur during a season. Older adults traveling to the southern hemisphere in April or May can be vaccinated; circulating influenza may be present in those communities.

The classic presentation of influenza is sudden onset of cough, fever, and myalgia.9 Other symptoms include chills, sore throat, runny nose, headaches, fatigue, and feeling feverish. Some adults have vomiting and diarrhea, but these symptoms are more common in children.10 As occurs in other infectious diseases, older persons, especially those who are frail, are less likely to present with a fever and more likely to present with acute confusion, also known as delirium.

Although the effectiveness of the influenza vaccine is reduced as a person ages, patients can achieve partial immunity with vaccination, thereby lessening severity of the flu.

Vaccine effectiveness
As mentioned previously, older patients often claim they caught the flu even though they got the flu shot. This is a common explanation for their decision not to get future flu shots. There are 2 reasons why this happens. The first is that not all influenza-like illnesses are true influenza. Actually, the evidence suggests that most influenza-like illness is not influenza. There are a host of viral and bacterial pathogens that cause flu-like illness with symptoms indistinguishable from those of true influenza. These include adenovirus, rhinovirus, respiratory syncytial virus, para-influenza virus, herpes simplex, and mycoplasma pneumonia.

In 1 study, 645 participants aged 60 years and older who reported influenza-like illness were tested for serologic infection. The study found that of the 109 participants who presented with the symptom complex of fever, coughing, and acute onset of illness, only 30.3% had serologic findings for acute influenza.11 Of the 105 who presented with the symptom complex of fever, coughing, acute onset of illness, and malaise, 29.5% had positive serologic findings. These 2 symptom complexes had the highest correlation to serologic infection.

It should be noted that approximately half the participants in the above study had received the annual flu vaccine, which brings us to the second reason older adults say they got the flu shot, but still got the flu. Older adults who get the flu shot can still contract true influenza. Despite this possibility, vaccination is still considered to be the most effective method for preventing both cases of influenza and its complications.12 It is generally believed the vaccine is 70% to 90% effective in preventing laboratory-confirmed influenza in young healthy adults.13,14 It is widely accepted that the vaccine is less effective in older patients because of immunosenescence.15,16 Although there is consensus the vaccine is worthwhile, there is debate on just how effective the vaccine is in older adults.

Most studies of the vaccine’s ability to prevent infection, hospitalization, or death are based on observational studies that typically use large research and health care utilization databases. A recent meta-analysis of these observational studies describes a host of difficulties for properly dealing with biases that overestimate as well as underestimate effectiveness.17 Only a very few prospective randomized controlled clinical trials have ever

Figure. Influenza vaccine priorities by risk of illness and transmission

<table>
<thead>
<tr>
<th>Highest Risk</th>
<th>Health care workers</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>Pregnant women</td>
</tr>
<tr>
<td></td>
<td>Newborns and children</td>
</tr>
<tr>
<td></td>
<td>Older adults</td>
</tr>
<tr>
<td></td>
<td>Individuals with comorbidities, including obesity</td>
</tr>
<tr>
<td></td>
<td>Individuals who have household contact with high-risk individuals</td>
</tr>
<tr>
<td></td>
<td>Individuals who are institutionalized, receiving long-term care, or have crowded living conditions</td>
</tr>
</tbody>
</table>

* The vaccine is indicated for all people 6 months or older who are at risk.
* Health care workers may be symptomatic or asymptomatic, and if they are sick, they should not provide health care.
explored the issue of the vaccine’s effectiveness in older persons. Perhaps the best of these found an effectiveness rate for preventing laboratory-confirmed influenza of 57% in persons between the ages of 60 and 69 years, and an effectiveness rate of 23% in persons aged 70 years and older.15

It should be remembered that vaccine effectiveness varies from year to year, based on the virus’s ever-shifting virulence and the closeness of the vaccine match to the virus that is circulating in the community. It also should be remembered that although effectiveness is diminished in older-age groups, those very patients also constitute a high-risk group who have much to gain from partial immunity. I often counsel older patients that even if the vaccine does not prevent the flu, it will lessen the severity of the flu.

There is growing evidence that the influenza vaccine offers more protection against cardiovascular disease than would be expected from prevention of the infection.19 It is well known that those with atherosclerotic cardiovascular disease are at increased risk for morbidity and mortality associated with influenza. Deaths from coronary heart disease surge following influenza epidemics and acute respiratory tract infections.20 Conventional thinking is that the physiologic stress associated with infection leads to higher cardiovascular morbidity and mortality. Some have made the case, however, that infection from influenza may pose a greater threat to persons with preexisting atherosclerotic disease than other infections.21 In mice with preexisting atherosclerotic plaques, the influenza virus caused the atherosclerotic vessels to become inflamed and thrombotic while healthy sections of aorta were unaffected.22 In another study, monocytes infected with influenza virus produced 3 to 5 times more pro-inflammatory cytokines interleukin-6 and interleukin-8 compared with cytomegalovirus and Chlamydia pneumoniae-infected cells.23 One clinical trial of 459 persons aged older than 50 years with known coronary artery syndrome found that after 12 months, those who received the influenza vaccine (9.5%) had significantly fewer deaths or hospitalizations from coronary artery syndrome, stroke, or heart failure relative to the control group (19.3%).24 Therefore, older adults with atherosclerotic cardiovascular disease may especially benefit from the annual flu vaccine.

Influenza vaccine side effects
Side effects from the flu shot is another major concern among older adults. The incidence of adverse reactions in persons aged older than 60 years has been studied in 1 randomized controlled clinical trial.25 In this study, 904 older adults received the inactivated trivalent vaccine and 902 received a placebo. The frequency of local reactions (swelling, itching, warm feeling, local pain, discomfort) was 17.5% in the vaccinated group and 7.3% in the placebo group ($P<.001$). The frequency of systemic reactions (fever, headache, malaise) was 11% for the vaccinated group and 9.4% for the placebo group ($P=.34$). The authors concluded that local reactions, all relatively minor, were more common in the vaccinated group than in the placebo group. Systemic reactions, however, were not more common in the vaccinated group than in the placebo group.

Who should not be vaccinated? The CDC recommends that the following individuals not be vaccinated: those with severe egg allergies, those with prior severe reaction to the vaccine, or persons with moderate to severe acute illness or a history of Guillain-Barré syndrome in the past 6 months. The link between Guillain-Barré syndrome and the flu shot remains unclear. In 1976 there was an additional case of Guillain-Barré syndrome for every 100,000 flu shots, but for other years the background case rate has been the same regardless of vaccination.26

Influenza vaccine and osteopathic manipulative treatment
A few prospective randomized controlled clinical trials have explored the efficacy of OMT to boost antibody titers to the influenza vaccine. Breithaupt and colleagues used a standardized thoracic lymphatic pump (TLP) protocol in which the practitioner applied 50 pumps per minute in rhythmic fashion for 5 minutes once a day for 4 days after vaccination.27 A hemagglutination inhibition assay measured antibody responses at baseline and at 4 weeks after vaccination. For young adults, 67% of 9 control subjects and 69% of the 16
TLP-treatment subjects had adequate antibody responses to the vaccine. For older adults, 31% of 26 control subjects and 36% of 28 TLP-treatment subjects had an adequate antibody response. There were no statistically significant differences between younger and older adults. In other words, the study failed to show any benefit from using the TLP protocol to boost antibody titers to the flu vaccine. There was a significant difference between the antibody response of younger adults vs that of older adults, which is consistent with findings from other clinical trials and observational studies.

A smaller randomized controlled clinical trial of 22 nursing home residents was conducted by Noll and colleagues. This exploratory study used a more sophisticated OMT protocol, which included a structural examination and specific treatment of somatic dysfunction, followed by a standardized sequence of 6 manipulation techniques (paraspinal inhibition, rib raising, myofascial release to the thoracic inlet, myofascial release to the abdominal diaphragm, thoracic lymphatic pump with activation, and splenic pump). The protocol was given 3 times a week for 2 weeks, then twice a week for 2 more weeks. The control group received a sham light-touch treatment for the same duration and frequency as the OMT group and was shown to be successful for blinding subjects to group assignment. The study found a weekly rise over 4 weeks in IgM and IgG antibody titers relative to baseline. However, there were no between-group differences in the antibody titers. Nevertheless, during the flu season the average days on antibiotics was 25 days (±20.6) for participants in the OMT group and 10.7 days (±16.1) for participants in the control group (P = .03). The study found a weekly rise over 4 weeks in IgM and IgG antibody titers relative to baseline. However, there were no between-group differences in the antibody titers. Nevertheless, during the flu season the average days on antibiotics was 25 days (±20.6) for participants in the control group and 10.7 days (±16.1) for participants in the OMT group (P = .03). A large multicenter clinical trial comparing clinical outcomes between the standard- and high-dose vaccines in older adults recently closed. The manufacturer’s website reports the high-dose vaccine was 24.2% more effective than the standard-dose vaccine in preventing influenza in adults aged 65 years and older. Secondary data analysis, however, is ongoing, and the manufacturer plans to submit a full clinical study report to the US Food and Drug Administration in early 2014. At present, the CDC does not endorse either of these newer options over the standard-dose inactivated trivalent vaccine.

### Older adults with atherosclerotic cardiovascular disease may especially benefit from annual influenza vaccines.

However, the high-dose vaccine also yields a higher rate of local injection site reactions, although systemic adverse reactions are comparable to those experienced with the standard-dose inactivated trivalent vaccine. It also remains unknown if the high-dose vaccine yields better clinical outcomes. The annual influenza vaccine remains a cornerstone of public health management of influenza. Because this virus is constantly changing, so is the biomedical community constantly updating the vaccine to keep the virus in check. Actual harms caused by the vaccine are minimal. Several exploratory clinical trials have tested the use of OMT to boost antibody response to the influenza vaccine and found no effect, but these studies are limited by their small size. Quadrivalent vaccines may broaden the protection received from the vaccine. More promising is a high-potency influenza vaccine for older adults, but full publication of clinical trials have failed to show any benefit from using the TLP protocol to boost antibody titers to the flu vaccine. There was a significant difference between the antibody response of younger adults vs that of older adults, which is consistent with findings from other clinical trials and observational studies.

A smaller randomized controlled clinical trial of 22 nursing home residents was conducted by Noll and colleagues. This exploratory study used a more sophisticated OMT protocol, which included a structural examination and specific treatment of somatic dysfunction, followed by a standardized sequence of 6 manipulation techniques (paraspinal inhibition, rib raising, myofascial release to the thoracic inlet, myofascial release to the abdominal diaphragm, thoracic lymphatic pump with activation, and splenic pump). The protocol was given 3 times a week for 2 weeks, then twice a week for 2 more weeks. The control group received a sham light-touch treatment for the same duration and frequency as the OMT group and was shown to be successful for blinding subjects to group assignment. The study found a weekly rise over 4 weeks in IgM and IgG antibody titers relative to baseline. However, there were no between-group differences in the antibody titers. Nevertheless, during the flu season the average days on antibiotics was 25 days (±20.6) for participants in the control group and 10.7 days (±16.1) for participants in the OMT group (P = .03). A large multicenter clinical trial comparing clinical outcomes between the standard- and high-dose vaccines in older adults recently closed. The manufacturer’s website reports the high-dose vaccine was 24.2% more effective than the standard-dose vaccine in preventing influenza in adults aged 65 years and older. Secondary data analysis, however, is ongoing, and the manufacturer plans to submit a full clinical study report to the US Food and Drug Administration in early 2014. At present, the CDC does not endorse either of these newer options over the standard-dose inactivated trivalent vaccine.

### New influenza vaccines

The common flu shot used in the older population for decades has been the inactivated trivalent vaccine. This vaccine contains antigens for the most likely strain of Influenza A H3N2, Influenza A H1N1, and Influenza B likely to be in circulation during the current flu season. There is now an inactivated quadrivalent vaccine that covers the same 3 viral strains plus an additional strain of influenza B. Theoretically, this formulation gives a broader range of protection. The other recent addition is a high-dose inactivated trivalent vaccine specifically marketed to patients aged 65 years and older. The high-dose vaccine contains 4 times the amount of antigen for each viral strain. Early studies show that this vaccine clearly yields higher antibody titers in older patients.

### Final notes

The annual influenza vaccine remains a cornerstone of public health management of influenza. Because this virus is constantly changing, so is the biomedical community constantly updating the vaccine to keep the virus in check. Actual harms caused by the vaccine are minimal. Several exploratory clinical trials have tested the use of OMT to boost antibody response to the influenza vaccine and found no effect, but these studies are limited by their small size. Quadrivalent vaccines may broaden the protection received from the vaccine. More promising is a high-potency influenza vaccine for older adults, but full publication of clinical trials have failed to show any benefit from using the TLP protocol to boost antibody titers to the flu vaccine. There was a significant difference between the antibody response of younger adults vs that of older adults, which is consistent with findings from other clinical trials and observational studies.

A smaller randomized controlled clinical trial of 22 nursing home residents was conducted by Noll and colleagues. This exploratory study used a more sophisticated OMT protocol, which included a structural examination and specific treatment of somatic dysfunction, followed by a standardized sequence of 6 manipulation techniques (paraspinal inhibition, rib raising, myofascial release to the thoracic inlet, myofascial release to the abdominal diaphragm, thoracic lymphatic pump with activation, and splenic pump). The protocol was given 3 times a week for 2 weeks, then twice a week for 2 more weeks. The control group received a sham light-touch treatment for the same duration and frequency as the OMT group and was shown to be successful for blinding subjects to group assignment. The study found a weekly rise over 4 weeks in IgM and IgG antibody titers relative to baseline. However, there were no between-group differences in the antibody titers. Nevertheless, during the flu season the average days on antibiotics was 25 days (±20.6) for participants in the control group and 10.7 days (±16.1) for participants in the OMT group (P = .03).

### Table. Influenza Vaccines

<table>
<thead>
<tr>
<th>Vaccine Category</th>
<th>Age indication</th>
<th>Number of antigens in vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated, intramuscular*</td>
<td>≥6 mo</td>
<td>3</td>
</tr>
<tr>
<td>Inactivated, intradermal</td>
<td>18-64 y</td>
<td>3</td>
</tr>
<tr>
<td>Recombinant, intramuscular*</td>
<td>18-49 y</td>
<td>3</td>
</tr>
<tr>
<td>High-dose inactivated, intramuscular*</td>
<td>≥65 y</td>
<td>3</td>
</tr>
<tr>
<td>Intranosal*</td>
<td>Live, attenuated</td>
<td>2-49 y</td>
</tr>
</tbody>
</table>

* Recommended site of vaccination is deltoid muscle.
* Suitable for healthy, non-pregnant persons.

outcomes from a multicenter comparison with the standard-dose vaccine is pending. Even though older adults have a diminished antibody response to the vaccine relative to younger adults, they are a high-risk group with much to gain from vaccination, especially those older adults with atherosclerotic cardiovascular disease. This dynamic means the vaccine is worthwhile for older adults.

References

Donald R. Noll, DO, is a practicing physician in Stratford, New Jersey, and professor at the Rowan University School of Osteopathic Medicine in the New Jersey Institute of Successful Aging. He is board certified by the American Osteopathic Board of Internal Medicine and by the American Osteopathic Board of Geriatric Medicine. Dr Noll can be reached at nolldr@rowan.edu.