The Centers for Disease Control and Prevention (CDC) has declared the decline in preventable diseases through vaccination to be 1 of the 10 great public health achievements in the past decade in the United States. Still, influenza epidemics occur every year in the United States and are associated with high rates of morbidity and mortality. A substantial portion of the US population chooses not to get vaccinated against influenza despite the illness and death associated with the disease. Low rates of vaccination are of particular concern in high-risk patients. The CDC’s Advisory Committee on Immunization Practices has broadened its influenza vaccine recommendations to include all individuals older than 6 months. Education of patients about the value of influenza vaccination will help to increase vaccination rates.

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Virus Characteristics
An improved understanding of the influenza virus and the vaccines available to prevent the disease may assist physicians in educating patients and improving vaccination rates. Influenza viruses are RNA viruses of the Orthomyxoviridae family. Two important surface proteins of the virus—hemagglutinin (HA) and neuraminidase (NA)—are responsible for part of the viral replication process, as well as the virus’s ability to mutate each year. These proteins are used to define the strains of influenza virus that are circulating in any given season. Hemagglutinin binds to sialic acid receptors on epithelial cells of the respiratory tract, allowing the virus to attach to the cell and penetrate the cell membrane. After viral replication inside the host cell, NA leaves the HA-receptor bond, allowing release of the virus.

The ability of HA and NA to change and to evade immune response is the reason that influenza can recur annually. The type of changes that occur in HA and NA are called antigenic drift and antigenic shift. Antigenic drift is caused by a mutation that alters HA or NA. Most of the altered viruses resulting from antigenic drift are noninfectious or are sensitive to circulating antibodies. However, if the mutant virus has changed enough to evade the immune system, a new, dangerous strain may emerge.

Antigenic shift is caused by genetic reassortment, resulting in a new virus strain, typically created by a genetic combination of components from 2 or more distinct influenza strains. Because influenza affects many species of animals,
reassortment may occur in other species before spreading to humans through contact with the infected animals. Antigenic shift is responsible for pandemics, which occur in the first few years after the development of a novel HA or NA to which the population does not have immunity. 

Three types of HA (H1, H2, H3) and 2 types of NA (N1, N2) are known to result in influenza pandemics among humans, though many more types are known to occasionally cause disease in humans. Antigenic shift does not occur with influenza type B viruses.

**Production of Vaccine**

Influenza vaccine production is based on inducing immune responses against HA or NA. Antibodies against HA prevent the virus from attaching to the host cell, and antibodies against NA prevent the release of the duplicated virus from the cell. Production of antibodies becomes adequate to protect against influenza infection approximately 2 weeks after vaccination. Within this 2-week period, the vaccinee may become infected with wild-type influenza viruses.

It is difficult to predict the immune response to influenza vaccines because many variables are involved, such as the age and immune status of the patient and antigenic drifting of the virus. A number of study designs have been used to measure many different outcomes. Although vaccine efficacy is measured during clinical trials, vaccine effectiveness cannot be determined until after widespread use of the vaccine in the general population. Among the clinical outcomes measured are numbers of days of illness, missed days of work, provider visits, hospitalizations, and deaths.

Immunologic responses, as measured with serologic testing, can be used to compare antibody levels produced by the current vaccine to antibody levels that correlate to clinical outcomes from previous seasons. However, that type of analysis is not as accurate as efficacy and effectiveness studies. A patient’s immunologic response to a vaccine may depend on a variety of factors, such as the age of the patient, the patient’s previous exposure to influenza antibodies, and the method used to measure the response. Other laboratory measures include rapid influenza testing and lateral culture.

At least 3 influenza viral strains have been identified in current circulation throughout the world, making vaccine production challenging. As the first step in virus identification each season, the World Health Organization, using epidemiologic surveillance, monitors circulating viruses around the world. Samples are then sent to several centers to identify the viruses.

After the circulating viral strains are identified, it takes months to develop the appropriate influenza vaccine. Typically in February, in the Northern Hemisphere, a rapidly growing influenza seed strain is prepared and tested for use in potential vaccines. The CDC in Atlanta, Georgia, is 1 of the centers where this testing takes place. After a vaccine is developed, it must be approved by the US Food and Drug Administration (FDA) before it can be produced and distributed in the United States.

### Vaccines for 2011-2012 Season

In July 2011, the FDA announced its approval of the vaccine formulation for the 2011-2012 season (Figure). The 3 viral strains selected for the vaccine are the following: A/California/7/09 (H1N1)-like virus; A/Perth/16/2009 (H3N2)-like virus; and B/Brissbane/60/2008-like virus. These are the same strains that were used in the 2010-2011 season. As always, it is possible that the selected strains may not match the actual influenza viruses that circulate during the influenza season. However, even if the vaccine strains are not an exact match to the circulating virus, the vaccine may reduce the severity of illness.

Between last season and this season, 2 new types of influenza vaccines became available—Fluzone High-Dose and Fluzone Intradermal. Fluzone High-Dose (Sanofi Pasteur Inc; Swiftwater, Pennsylvania) was introduced in the 2010-2011 influenza season. This vaccine, which contains 4 times the amount of antigen against the 3 selected strains as does regular-dose Fluzone, is indicated for use in adults aged 65 years or older. The high dose is designed to benefit elderly patients, who do not respond to influenza vaccines as well as young, healthy individuals. Fluzone High-Dose induced higher antibody titers than the regular-dose formulation when measured by HA inhibition and neutralizing antibodies.

Local adverse events (eg, redness, swelling, pain) were more common in patients given the high-dose Fluzone formulation than in patients given regular-dose Fluzone. The ACIP currently does not recommend using Fluzone High-Dose over regular-

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### Table: Proprietary Name, Manufacturer, and Approved Age

<table>
<thead>
<tr>
<th>Proprietary Name</th>
<th>Manufacturer</th>
<th>Approved Age*</th>
</tr>
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<tbody>
<tr>
<td><strong>Trivalent Inactivated Influenza Vaccine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluarix</td>
<td>GlaxoSmithKline Pharmaceuticals, Research Triangle Park, NC</td>
<td>≥3</td>
</tr>
<tr>
<td>FluLaval</td>
<td>ID Biomedical Corporation, Laval, Quebec</td>
<td>≥18</td>
</tr>
<tr>
<td>Fluvirin</td>
<td>Novartis Pharmaceuticals, East Hanover, NJ</td>
<td>≥4</td>
</tr>
<tr>
<td>Fluzone (regular dose)</td>
<td>Sanofi Pasteur, Swiftwater, PA</td>
<td>≥6 mo</td>
</tr>
<tr>
<td>Fluzone High-Dose</td>
<td>Sanofi Pasteur, Swiftwater, PA</td>
<td>≥65</td>
</tr>
<tr>
<td>Fluzone Intradermal</td>
<td>Sanofi Pasteur, Swiftwater, PA</td>
<td>18-64</td>
</tr>
<tr>
<td><strong>Live Attenuated Influenza Vaccine</strong></td>
<td></td>
<td></td>
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<tr>
<td>FluMist</td>
<td>Medimmune, Gaithersburg, MD</td>
<td>2-49</td>
</tr>
</tbody>
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*Figure. Influenza vaccines approved by the US Food and Drug Administration for the 2011-2012 season, listed by proprietary name, manufacturer, and age of vaccinee. These vaccines are designed with 3 viral strains: A/California/7/09 (H1N1)-like virus; A/Perth/16/2009 (H3N2)-like virus; and B/Brissbane/60/2008-like virus. * Ages are shown in years unless otherwise indicated.
dose influenza vaccine because no randomized, controlled studies are available to demonstrate greater clinical efficacy of the high-dose formulation.

Fluzone Intradermal (Sanofi Pasteur Inc) is being introduced in the 2011-2012 influenza season. This vaccine contains 27 μg of antigen in 0.1 mL of vaccine, compared to 45 μg of antigen in 0.5 mL of regular influenza vaccine. It is available in a special syringe to allow it to be administered intradermally. Fluzone Intradermal is indicated for use in adults aged 18 to 64 years. In safety and antibody titer studies comparing Fluzone Intradermal to regular Fluzone, antibody titers were not inferior with intradermal administration, though seroconversion rates against influenza type B virus were slightly lower with the intradermal vaccine. Injection site adverse reactions, though not serious, were also more common with intradermal administration. Continued Challenges

Vaccination against influenza remains the most effective method to prevent infection and its complications. The rapid mutation of the influenza virus makes the development of effective vaccines an annual challenge. Furthermore, it is often difficult to convince patients of the importance of vaccination. Many patients underestimate the risk of influenza infection and overestimate the risk of adverse effects of the vaccine. In recent years, new settings for vaccination have become available, such as pharmacies and community centers, improving public access to vaccination. It is important for physicians and other healthcare providers to offer vaccination at every opportunity.

Healthcare personnel are themselves at risk of acquiring influenza infection and of transmitting influenza to patients, visitors, and coworkers. Healthcare personnel have an ethical and professional obligation to help prevent the spread of influenza by making sure that they get immunized every year. Unfortunately, the percentage of healthcare personnel who get vaccinated is rather low—though there has been an upward trend in vaccination rates in recent years. According to the CDC, the uptake of influenza vaccine among healthcare personnel was 44.4% in 2006-2007, 49.0% in 2007-2008, and 65% in 2009-2010. The Healthy People 2020 recommendations set a goal of 90% influenza vaccination coverage for healthcare workers. To reach that goal, most healthcare facilities will need to mandate vaccination for their personnel and to institute comprehensive infection control and education programs.

Conclusion

While the search for better vaccines continues, the ever-changing nature of the influenza virus will continue to present a challenge. Vaccine production has improved, and quantities of vaccine have increased each year. However, large amounts of unused vaccine are destroyed at the end of each influenza season. Education and encouragement of patients regarding the value of influenza vaccination will help to increase vaccination rates.

References

8. Nichol KL. The efficacy, effectiveness and cost-effectiveness of inactivated influenza virus vac-