New options for influenza vaccines: Quadrivalent, recombinant, and cell culture

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After 2 years of relatively mild influenza seasons, the 2012–13 season was more severe. The extremes of age were particularly hard hit, with 154 pediatric deaths reported and hospitalizations in individuals 65 years or older reaching a rate of 172 per 100,000. Influenza A H3N2 predominated early in the season, then influenza type B became more prevalent. Although vaccination is established as one of the most effective methods in preventing influenza, limitations exist. Several new vaccines help overcome some of these barriers (Table 1).

Quadrivalent vaccines

Since 1975, the standard seasonal influenza vaccine has been a trivalent vaccine that consists of two strains of influenza A (H1 and H3) and a single strain of influenza B. In previous years, however, bi-, quad-, penta-, and hexavalent formulations were distributed at various times.

In recent years, two type B lineages (known as Victoria and Yamagata) have taken turns in predominating, but strains of both often have circulated to some extent in any given year. Vaccination against a single B lineage strain provides limited cross-protection against strains within the other lineage that also is circulating in the population. In 6 of the previous 12 influenza seasons, the B lineage component of the trivalent influenza vaccine (TIV) did not match the major circulating B strain, affording limited protection from infection. Infection with influenza B is a major cause of clinic visits, hospitalizations, and death among all age groups. Hospitalization may be more common in pediatric patients infected with type B compared with type A influenza. The type B viruses cause approximately 20% to 25% of infections and lead to influenza epidemics every 2 to 4 years, making adequate protection from both lineages vital in optimizing prevention against seasonal influenza.

The newly developed four-component or quadrivalent influenza vaccines (QIVs) contain both B lineages. Composed of hemagglutinin from A/H1N1, A/H3N2, and the antigenically distinct B/Victoria and B/Yamagata subtypes, widespread use of these vaccines can result in reduction in negative outcomes associated with influenza infection.

Flumist live attenuated QIV (MedImmune) currently is approved for individuals aged 2 through 49 years and is the first vaccine to contain all four strains of the influenza virus. Two randomized, double-blind, active-controlled, multicenter trials demonstrated noninferiority of FluMist QIV compared with current TIV based on geometric mean titers (GMTs) of anti-influenza antibody. The safety profile is similar to FluMist TIV, including serious adverse events. Post hoc subgroup analyses of immunogenicity and serious adverse events by sex, race/ethnicity, and age did not show significant differences among groups.

Fluzone QIV (Sanofi Pasteur) was licensed for individuals older than 6 months in June 2013 for the 2013–14 influenza season. GMT, rates of seroconversion and seroprotection, and safety profile were comparable with Fluzone TIV in three clinical studies. The majority of serious adverse events were reported as unrelated to vaccination.

Fluarix QIV (GlaxoSmithKline) was licensed in December 2012 for the 2013–14 influenza season. Intramuscular vaccine is approved for patients 3 years of older. Two randomized, double-blind, active-controlled safety and immunogenicity studies with antigenically matched strains demonstrated noninferiority to current Fluarix TIV.

Although a strong antigenic match cannot be completely ensured in any given year, the addition of a second B lineage decreases the likelihood of a mismatch in lineage between the vaccine viral strains and circulating strains. The additional public health benefit of adding a second influenza B strain was evaluated by Reed et al. using an epidemiologic model to estimate the impact of a QIV compared with TIV over 10 previous influenza seasons (1999–2009). They found that use of a QIV could have reduced annual cases by 2,200 to 970,000, hospitalizations by 14 to 8,200, and deaths by 1 to 485 in the United States; however, the production capacity necessary to create a QIV could reduce vaccine availability if demand was great enough. Reed et al. concluded that the additional protection provided by including a second influenza B strain could lead to a modest reduction in influenza-related outcomes.

Recombinant (egg-free) vaccine

Although rare, severe allergic reactions, including life-threatening
anaphylaxis, can occur as a result of several components of the seasonal influenza vaccine. As with all vaccines, those with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine should not receive it. The Centers for Disease Control and Prevention (CDC) recommend that patients who have experienced only hives or other skin reactions to egg products receive the influenza vaccine with additional safety measures. The newly licensed recombinant influenza vaccine offers an option for individuals who were unable to be immunized because of severe allergy.

Flublok (Protein Sciences) is an intramuscularly administered single-dose TIV licensed in January 2013 for use in patients 18 through 49 years of age. Recombinant influenza hemagglutinin is produced in an insect cell line of the armyworm. The vaccine avoids direct use of the influenza virus or egg proteins in its manufacturing. Theoretically, this technology presents the potential for more rapid vaccine production in the event of a pandemic. Flublok was required to undergo standard immunogenicity studies and additional efficacy evaluations because the vaccine contained hemagglutinin protein only, with no neuraminidase present. Two randomized placebo-controlled clinical trials demonstrated injection site reactions and other adverse effects that were similar to conventional inactivated, egg protein–based vaccines. Because of the nature of Flublok’s manufacturing, the injection has a shelf life of only 16 weeks.

### Cell culture vaccine

Flucelvax (Novartis) is an intramuscularly administered single-dose...
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TIV approved in October 2012 for use in individuals 18 years or older. The vaccine virus is cultured at industrial scale in mammalian animal cells instead of eggs. However, the seed virus used to produce each batch of vaccine is initially cultured in chicken eggs; therefore ACIP has not deemed the vaccine completely egg free (June 2013 Advisory Committee on Immunization Practices meeting). An evaluation in a multinational, randomized, controlled study demonstrated more than 80% effectiveness versus placebo. Safety data were assessed through seven multinational, randomized, controlled studies with adverse effects typical of those with other injectable influenza vaccines.

Summary
The QIV offers certain advantages for preventing influenza by expanding the degree of viral protection to two B lineage viruses, while the egg-free and cell culture vaccines present safe options for patients with severe egg allergy and may expand vaccine supply.

References