INFLUENZA GUIDE FOR PHARMACISTS
JULY 2022

After a Rare Mild 2020-2021 Season, Influenza Is Back

Influenza Vaccine Technologies: What’s New to Fight the Flu

The Role of the Ambulatory Care Pharmacist in Promoting Vaccine Confidence

Influenza Activity and Vaccine Effectiveness During the 2021-2022 Season

Examining the Public Health Impact of Pharmacies as Additional Sites for Rapid Diagnostic Testing

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During the week ending July 16, 2022, some 400 to 2400 new hospital admissions of patients with influenza likely will be confirmed and reported throughout the United States. In comparison, rates of influenza infection were nearly negligible during the 2020-2021 season. This, perhaps, is not surprising, since there was a partial shutdown of the United States and many COVID-19 countermeasures were in place over that period. Disease spread likely was mitigated by even stronger countermeasures in Southeast Asia, where influenza’s annual migration to the Americas may begin. Travel was suppressed, and vaccination rates for influenza among adults were the highest ever recorded, cresting 50% for the first time.

During that 2020-2021 season, pharmacies surpassed doctors’ offices to become the most frequent sites of care for adult influenza vaccine administration, and pharmacy staff delivered more than one-third (39%) of all adult vaccines. The 2021-2022 season has been associated with far fewer rates of infection and hospitalization than noted during prior seasons, yet influenza infection rates remain high; pharmacists need to remain vigilant throughout these summer months.

HIGH HOSPITALIZATION RATES LINGER
This 2021-2022 season has produced a substantial, though lower than average, rate of hospitalizations. Data from the CDC indicate a typical rise in hospitalizations over the winter holidays, followed by a drop in hospital admissions, a steady gain starting in the beginning of February, a peak in early May, and a rate of hospitalizations that has remained above 2000 cases per week ever since (Figure 1). We are not out of the woods this season; rather, Americans are being hospitalized for influenza at rates similar to those seen over the winter holidays. Interestingly, this spring’s rise in hospitalization rates coincides with reduced COVID-19 countermeasures and a broader “opening up” of the country.

LATE INFLUENZA SEASON CAUSES AN EXTENSION OF SURVEILLANCE INTO THE SUMMER
The Influenza Hospitalization Surveillance Network (FluSurv-NET) consortium provides flu-based surveillance for the CDC. Owing to the late-season rise in influenza cases and hospitalizations, the consortium’s
monitoring has been extended beyond week 17 (April 30) for the first time (Figure 2). Bottom line: We’re still in the 2021-2022 flu season, and patients should be assessed and treated accordingly.

**AFTER 2 MILD INFLUENZA SEASONS, ARE WE DUE FOR A MORE TYPICAL 2022-2023?**

Influenza hospitalization rates are lower this season than during those spanning the past decade.\(^8,9\) However, with easing of COVID-19 restrictions, we have the potential to experience the first flu season in 3 years without having significant respiratory countermeasures in place.\(^10,11\) Will influenza become the main driver of infection-related morbidity and mortality, potentially outpacing COVID-19 by the fall? Currently, COVID-19 hospitalizations have risen steadily past their pandemic lows, and it’s anyone’s guess what the summer and fall will hold.\(^12\)

**HOW WILL COVID-19 VACCINATIONS AFFECT 2022-2023 INFLUENZA VACCINATIONS?**

Although the 2020-2021 season brought the highest influenza vaccination rates ever, the 2021-2022 season thus far seems to have resulted in slightly lower rates of influenza.\(^4,13\) Widespread access to and administration of COVID-19 vaccination(s) may have provided a bit of a boost to the use of influenza vaccinations, as well. Will this fall bring additional COVID-19 boosters? Will people be lax...
with influenza vaccinations after 2 mild seasons? What about test-to-treat? Will pharmacists gain greater authority or maintain test ordering services with the same level of access and intensity for respiratory infections as they had with COVID-19?

DON'T FORGET: REIMBURSEMENT FOR NON–COVID-19 VACCINE ADMINISTRATION INCREASES SUBSTANTIALLY FOR MEDICARE PATIENTS

Regardless, the Centers for Medicare & Medicaid Services (CMS) has made outreach, counseling, and, ultimately, administration of the influenza vaccination more sustainable. Starting on January 1, 2022, CMS nearly doubled the Part B vaccination reimbursement to $30. This move should incentivize pharmacies across the country to become even more vigilant about helping to get that rate of adult vaccine administration back above 50% and beyond. There may or may not be a COVID-19 vaccination push in the fall. Either way, we need to ready our pharmacies for flu vaccine campaigns and to take care of patients—and our community—during the current season.

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Influenza Vaccine Technologies: What’s New to Fight the Flu

By LAUREN B. ANGELO, PHARMD, MBA

As the world continues to navigate the ups and downs of the COVID-19 pandemic, one thing remains certain—influenza is still a threat. Although influenza cases were at record lows during the 2020-2021 season when pandemic precautions and stay-at-home orders were in place, the numbers crept back up during the 2021-2022 season as these measures were lifted.\(^1,2\) Preliminary estimates from the CDC indicate that there were 82,000 to 170,000 hospitalizations and 5000 to 14,000 deaths associated with influenza between October 1, 2021, and June 11, 2022.\(^2\) Influenza surveillance does not capture all cases of flu that occur; therefore, the CDC produces this estimated range of cases to better reflect the greater burden of influenza in the United States.\(^2\)

Influenza A (H3N2) has accounted for nearly all specimens tested during the 2021-2022.\(^4\) On March 3, 2022, the FDA endorsed the World Health Organization (WHO) recommendations for the 2022-2023 influenza vaccine composition, which applies to egg-, cell culture-, and recombinant-based vaccines.\(^4,5\) As has been the case for many years, the WHO recommended that quadrivalent vaccines target 2 influenza A strains (H1N1 and H3N2) and 2 B strains.\(^6,4\) The recommended strains are based on global surveillance data and are not always a good match for the strains that ultimately circulate during the impending season. This mismatch and, consequently, low vaccine effectiveness may be due to antigenic drift in circulating viruses and/or egg-adaptive mutations that occur during the manufacturing of egg-based vaccines.\(^4,9,10\) Investigators are determined to find influenza vaccines that circumvent these challenges and demonstrate greater vaccine effectiveness. New manufacturing technologies and the development of a universal influenza vaccine have been at the forefront of this research.

STATUS OF A UNIVERSAL INFLUENZA VACCINE

The National Institute of Allergy and Infectious Diseases (NIAID) within the National Institutes of Health has outlined a strategic plan for the development of a
universal influenza vaccine.\textsuperscript{11} Making this one of its highest priorities, the NIAID budgets $220 million annually in the hopes of identifying a vaccine that is\textsuperscript{11-13}:

- highly effective ($\geq 75\%$);
- long-lasting ($\geq 1$ year of protection);
- suitable for all age groups; and
- able to cover multiple influenza strains, including those that could lead to a pandemic.

To meet these criteria, the NIAID has called for a vaccine that provides protection against groups 1 and 2 influenza A viruses, which account for 18 subtypes (H1-H18).\textsuperscript{11,14} Type A viruses have been solely responsible for influenza pandemics. H1 (H1N1) and H3 (H3N2) have been co-circulating for years and, along with the influenza B/Victoria lineage and influenza B/Yamagata lineage viruses, are responsible for seasonal influenza infections.\textsuperscript{15} However, H2, H5, H6, H7, H9, and H10 also have caused human infections and deaths, and they are considered potential threats. A universal influenza vaccine ideally should target all of these subtypes.\textsuperscript{16}

In addition, the NIAID suggests that a universal influenza vaccine induce antibodies that target other components of the virus, such as the stalk of the hemagglutinin (HA) protein. This protein on the outer surface of the influenza virus allows it to attach to a human cell (Figure).\textsuperscript{15} It has a head and a stalk. The head is considered to be the immunodominant domain; it is responsible for most of the escape mutations seen with the virus.\textsuperscript{14} The stalk is more stable, and it remains relatively unchanged; however, its immune response is less robust. The seasonal influenza vaccines currently in use induce antibodies that target the head domain and, as a result, the strains in the vaccine often need to be changed each year to account for antigenic drift. A universal influenza vaccine that targets the stalk while still eliciting a robust immune response has been the focus of recent research.\textsuperscript{17} Other studies have begun exploring either neuraminidase or the bottom of the stalk (ie, the anchor) as targets.\textsuperscript{18} Chimeric HA technology has been proposed to induce stalk-specific antibodies; however, underwhelming results from phase 1 clinical trials prompted GlaxoSmithKline to halt development of its chimeric HA universal influenza vaccine.\textsuperscript{19,20}

The NIAID has several exploratory and phase 1 clinical trials underway.\textsuperscript{21-23} Most recently publicized is the phase 1 trial of FluMos-v1, a nanoparticle influenza vaccine designed to stimulate antibodies against multiple strains.\textsuperscript{21} In addition to eliciting antibodies against the 4 strains targeted in seasonal vaccines, FluMos-v1 displays multiple copies of the HA types. The results of animal studies demonstrated additional protection against H5 and H7, which are not in the seasonal vaccine.\textsuperscript{24}

BiondVax is also making strides towards a universal vaccine. Its investigators have been researching a universal vaccine for more than 10 years.\textsuperscript{25} BiondVax's “multimeric” vaccine is a recombinant protein containing 9 conserved, common linear influenza epitopes that activate both cellular and humoral immunity against a wide variety of influenza A and B strains. Studies have been conducted in Eastern Europe; the research currently is in various phases, including phase 3 trials.\textsuperscript{26-28}

**Challenges With Universal Influenza Vaccine Research**

Large-scale efficacy studies for a universal vaccine have been challenging to conduct.\textsuperscript{17,25} A person’s age may contribute to their preexisting immunity to different influenza strains. Prior exposures may impact the ability to generate protective antibodies that target the HA stalk.\textsuperscript{26} Clinical trials would need to include a range of age groups; manufacturers may then need to develop age-specific vaccines. Comparing such a universal vaccine to those currently licensed for seasonal influenza has its shortcomings; it’s akin to comparing apples to oranges. To be approved, the vaccine will likely need to demonstrate in clinical studies its impact on clinical infection, hospitalizations, and death. Such research takes time and money. Additionally, manufacturers will need to stay ahead of drifted and shifted strains as the product advances through the trial phases. More advanced manufacturing platforms (eg, nanoparticle messenger RNA [mRNA], adenovirus-vector, cell-based, and recombinant technologies) will likely be key for targeting different components of the virus and eliciting more robust T-cell immunity.

**mRNA-BASED INFLUENZA VACCINES**

When people encounter the term mRNA vaccines, they may think of COVID-19 vaccines. However, mRNA technology for vaccine development predates the emergence of SARS-CoV-2 by at least a decade.\textsuperscript{29,30} This initial research provided the knowledge and framework needed to rapidly develop COVID-19 vaccines. Safety, efficacy, and rapid scalability have been the focal points of mRNA vaccine research. These 3 factors are critical when developing new
influenza vaccines, especially if an influenza pandemic unexpectedly emerges. Several companies, including Moderna, GlaxoSmithKline, Sanofi Pasteur, CureVac AG, and Pfizer, have been conducting clinical trials in healthy adults to assess the safety and efficacy of seasonal influenza mRNA vaccines, which include monovalent, bivalent, and quadrivalent formulations.\textsuperscript{10-13} Moderna has several mRNA influenza vaccines in development, and interim phase 1 data have been released for its quadrivalent seasonal vaccine.\textsuperscript{34} Immunogenicity data for the 4 strains were promising, but there is concern that the increase in antibody titers was comparable to that of currently available vaccines.\textsuperscript{35} Phase 2 trials aim to assess dosing and provide a head-to-head comparison with an approved vaccine. To get ahead of the next influenza pandemic, Moderna has also explored vaccines that target the avian strains H10N8 and H7N9; these were evaluated for safety and efficacy in phase 1 trials and found to be well-tolerated and to offer robust humoral immunity.\textsuperscript{36}

One of the benefits of mRNA technology is that it does not rely on cell cultures or chicken eggs for vaccine production. Other potential benefits afforded by mRNA influenza vaccines include high fidelity, meaning that they can provide an exact antigen match to the influenza strains recommended for the vaccine, the ability to target different components of the virus, induction of T-cell immunity, and faster production time, which allows companies to wait to begin manufacture to ensure a better match to circulating strains. The mRNA influenza vaccines may have disadvantages similar to those of COVID-19 mRNA vaccines; these include short-term protection and a higher incidence of local and systemic effects (due in part to the lipid nanoparticle component necessary to provide vaccine stability and delivery into cells).\textsuperscript{31,37}

Research on the mRNA vaccine has been expanded to assess the impact of encoding for the HA stalk, neuraminidase, matrix-2 ion channel, and nucleoprotein (Figure).\textsuperscript{15,31} This may also pave the way for potential universal influenza vaccines.

**CELL-BASED AND RECOMBINANT VACCINE UPDATES**

Cell-based and recombinant influenza vaccines were first licensed in the United States in 2012 and 2013, respectively. Cell-based vaccines do not rely on chicken eggs.\textsuperscript{38} Rather, the manufacturer inoculates mammalian cells using the candidate vaccine viruses (CVVs) that were grown in cells. After the CVVs replicate, they are extracted from the cells to make the vaccine. Recombinant vaccines are synthetic and do not use CVVs. The gene for making HA is combined with a baculovirus, resulting in a recombinant baculovirus that is introduced to a host cell line. The cells are instructed to produce the HA antigen, which is used to make the vaccine.\textsuperscript{38} Recombinant protein vaccines, like mRNA vaccines, can provide an exact match to the antigens in the strains recommended for the respective season’s influenza vaccine. However, the manufacturing process for recombinant protein vaccines is more complex than it is for mRNA vaccines.\textsuperscript{31}

Flucelvax Quadrivalent (Seqirus, Inc) is the only cell-based influenza vaccine licensed for use in the United States. It is a quadrivalent vaccine, and its approval was recently expanded for use in individuals aged 6 months and older.\textsuperscript{39} FluBlok Quadrivalent (Protein Sciences Corporation, a Sanofi company) is currently the only quadrivalent recombinant influenza vaccine available in the United States; it is approved for use in adults (age ≥ 18 years).\textsuperscript{40} Another recombinant vaccine is currently in development. Made by Novavax, Inc., NanoFlu is being tested in phase 3 trials.\textsuperscript{41} In an attempt to induce a T-cell response, which would give this quadrivalent vaccine a potential advantage over FluBlok Quadrivalent, a novel
adjuvant (Matrix-M) has been added. NanoFlu contains 60 µg of recombinant HA per each of the 4 strains. This is more than in Flublok Quadrivalent, which contains 45 µg of HA per strain, and in a standard-dose inactivated influenza vaccine, which contains 15 µg of HA per strain. When compared with the standard-dose quadrivalent inactivated influenza vaccine, NanoFlu demonstrated enhanced humoral and cellular immune response in adults aged at least 65 years. Its safety profile was comparable overall. Injection site pain was reported more frequently in the NanoFlu group than in individuals given standard-dose inactivated influenza vaccine (25.6% vs 16.1%); this is consistent with the higher incidence of local reactions often reported for adjuvanted vaccines. It is not yet known how NanoFlu compares with other quadrivalent influenza vaccines that are specifically marketed for use in older patients (adjuvanted influenza vaccine, Fluid Quadrivalent [Seqirus]; high-dose influenza vaccine, Fluzone-HD Quadrivalent [Sanofi]). As they noted in an editorial, investigators comparing the trivalent formulation (tNIV) with the trivalent high-dose influenza vaccine in adults aged 60 years and older found that the tNIV induced substantially greater antibody responses against 4 H3N2 strains while maintaining a similar safety profile. Next steps for Novavax include clinical efficacy studies for NanoFlu.

INFLUENZA AND COVID-19 VACCINE COMBINATION

Considering the anticipated emergence of new SARS-CoV-2 variants and the waning immunity of the COVID-19 vaccines, FDA and CDC officials along with vaccine manufacturers have speculated that recurring COVID-19 vaccine boosters will be needed. Combining such boosters with seasonal influenza vaccination has become a strategy that some vaccine manufacturers, most notably Moderna and Novavax, have set in motion. Moderna announced to its investors plans to develop 2 respiratory combination vaccines: 1 that encodes for the SARS-CoV-2 spike protein and influenza HA glycoproteins, and 1 that targets the SARS-CoV-2, influenza, and respiratory syncytial viruses. Novavax is conducting a phase 1/2 study to assess NanoFlu combined with its recombinant nanoparticle COVID-19 vaccine coformulated with the Matrix-M adjuvant (NVX-CoV2373). NVX-CoV2373 was granted the WHO’s emergency use listing under the brand names Covovax and Nuvaxovid; however, emergency use authorization for use of the vaccine in the United States is pending.

With so many new technologies and approaches being explored to prevent influenza, it is likely that the market will see an increase in the number and type of influenza vaccines available over the next 1 or 2 years. Whether these technologies lead to a universal vaccine that meets the NIAID criteria or simply an enhanced seasonal vaccine remains to be determined.

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Vaccines represent a cost-effective means of preventing illness, complications, and death from certain diseases. Nonetheless, across the health care system there remain challenges in promoting vaccine acceptance and addressing hesitancy and patient concerns. This article explores the role of ambulatory care pharmacists in addressing patient concerns to promote influenza vaccine acceptance.

THE AMBULATORY CARE CLINIC AS A VACCINATION DESTINATION

Ambulatory care, according to the Board of Pharmacy Specialties, is a field that addresses the delivery of integrated, accessible health care services for ambulatory patients moving from the hospital to home or another health care facility. Ambulatory care can encompass a wide range of disciplines and populations, and some may describe it as the “internal medicine of the outpatient setting.” There may be ambulatory care pharmacists in family medicine clinics, pediatric or geriatric clinics, or in medical specialty clinics.

A pharmacist’s role in the ambulatory care setting has traditionally included a review of medications for potential drug-drug interactions and adverse events, medication reconciliation, and the provision of counseling services. Although the scope of the ambulatory care pharmacist’s role may vary according to local practice and different ambulatory clinic service models, ambulatory care pharmacists can initiate, adjust, or discontinue medications, monitor clinical laboratory studies, and assess patients’ vaccination history.

Case Study

A 34-year-old woman is referred to a clinic for treatment of hepatitis C infection. She gave birth a few weeks prior to her visit. She has a previous history of intravenous drug use but has no other chronic health conditions. Aside from suggesting appropriate therapy for hepatitis C infection, recommended immunizations were discussed. The following immunizations are advised today for this patient: hepatitis B, influenza, and COVID-19 vaccines. This is how the interaction unfolds:

Pharmacist: Hello, it’s good to see you again! You are eligible for the influenza vaccine today. Would you like to receive it while you are here in the clinic?

Patient: No! Absolutely not. I have heard so many negative things about the flu vaccine and I do not want to get it at this time. I don’t want to hear anything else about the flu vaccine.

Pharmacist: OK. You are also eligible to receive the hepatitis B vaccine. Are you interested in receiving this vaccine while you are here today?

Patient: Yes, sure. I will get that vaccine while I am here.
all 50 states, although some states may have specific vaccine exemptions and limitations on the pharmacist scope of vaccine services. The accessibility of pharmacists increases opportunities for patients to receive vaccines, expands pharmacists’ scope of practice, and promotes continuity of care across the health care setting. In some ambulatory care clinics, identifying appropriate immunizations for patients may be an expectation, and in others it may serve as a metric of quality improvement and patient safety.

**IMPACT AND CONSIDERATION OF VACCINE QUALITY MEASURES FOR THE HEALTH CARE SYSTEM**

As health care delivery increasingly transitions to and incentivizes value-based care, ambulatory care pharmacists are poised to impact patient outcomes as members of the interprofessional care team. In the United States, the influenza vaccination rate remains low in adults 18 to 49 years of age (37.7%), with higher rates observed in older adults. For the 2020-2021 influenza season, influenza vaccination coverage among adults (≥ 18 years) was 50.2%. Offering influenza vaccination to eligible patients represents an important indicator of quality care and preventative medicine for both ambulatory and hospitalized inpatients according to the Centers for Medicare & Medicaid Services and The Joint Commission, respectively.

**ADDRESSING VACCINE HESITANCY AND SUPPORTING VACCINE CONFIDENCE**

Vaccination uptake—or acceptance—is driven by several factors. The World Health Organization (WHO) defines vaccine hesitancy as a delay in acceptance or the refusal of vaccines despite availability of vaccine services. Vaccine hesitancy may depend on time, place, and particular vaccine. It is influenced by factors known as the “3 Cs” of complacency, convenience, and confidence. The WHO’s vaccine hesitancy model is depicted as 3 overlapping ovals, with each oval representing 1 of the 3Cs. Research has demonstrated that anecdotal evidence is often more influential than facts and science in informing patient vaccination decisions. This can make it difficult to discuss with patients the importance of immunizations when there are several factors influencing the decision to obtain a vaccine (eg, social media, news, etc). This model also emphasizes the multifaceted nature of vaccine hesitancy.

In contrast to vaccine hesitancy, according to the CDC, vaccine confidence is the belief that vaccines work, are safe, and are a component of a trustworthy medical system. It is imperative that health care providers recognize the multiple factors that influence patient vaccine decision-making. The CDC offers resources for health care professionals to support vaccinating with confidence. Largely geared toward the acceptance and promotion of the COVID-19 vaccines, this framework provides a means to strengthen patient confidence in vaccines to prevent outbreaks of vaccine-preventable disease. To empower patients to have vaccine confidence, the CDC model references the following strategies: building trust, empowering health care personnel, and engaging communities and individuals (Figure).

The foundation of vaccine confidence starts with building trust; this is accomplished by the health care professional sharing a clear, complete, and accurate message about vaccines. The goal is to build trust not only with the vaccine but also in the vaccinator and the health care system in coordination with various partners. Empowering health care personnel to promote their decision to be vaccinated and recommending vaccination to their patients is an important step in building vaccine confidence. Engaging communities and individuals in vaccine confidence can build trust, encourage communication, and increase collaboration.

Combining the accessibility and role of the ambulatory care pharmacist with the importance of combating vaccine hesitancy opens a world of possibilities for engaging patients to receive any vaccine, including the influenza vaccine. The first inactive influenza vaccines became available for use in the 1940s. Although community pharmacists have been offering and administering patient immunizations for more than 25 years, the pharmacist’s role in promoting vaccine confidence continues to evolve, particularly in recent years. In an editorial by Petrelli and colleagues, they discuss the pivotal role of pharmacists in providing health information, vaccinations, and fostering health promotion.

Although the editorial was published in 2019, many examples of vaccine hesitancy that are discussed still hold true today. The authors describe pharmacists as influential health care providers who can focus their efforts on patients who are uncertain and supply them with objective, scientific, and legal tools which are valuable yet underused.

As mentioned previously, the role of the ambulatory care pharmacist is unique and provides an additional point of connection that might not translate in the traditional doctor-provider relationship. The ambulatory care pharmacist can be a liaison between the provider and the patient, with more accessibility, flexibility with time, and the sense of an added advocate for the patient and provider. The ambulatory care pharmacist is also poised to combat specific influenza vaccine myths and misperceptions (Table 1) and instill vaccine confidence to protect their patients from vaccine-preventable illness.
CASE STUDY REVISITED
The presenting patient has vaccine hesitancy and lacks vaccine confidence. In her interaction with the pharmacist, she agrees to receive the hepatitis B vaccine but not the influenza vaccine and appears to be comfortable with her decision to choose one vaccine over another. She is complacent with not getting a vaccine during her visit, given the negative information that she has received about the influenza vaccine. Although it would be convenient for her to get 2 vaccines at this visit, she respectfully declines at this time. Her confidence in the hepatitis B vaccine outweighs her confidence in the influenza vaccine. Although there was no reason provided in this interaction, her tone and voice change when the influenza vaccine is brought up. In this patient’s case, the pharmacist could leverage this patient’s vaccine confidence in the following ways:

(1) **Build trust with the patient:** Refrain from being judgmental. Listen to the patient and their concerns. In building trust, it would be important to know the situation in which the patient would be most comfortable receiving both vaccines.

(2) **Empower health care providers:** Trust in vaccines is a key aspect for fostering patient confidence and acceptance of indicated vaccines. The ambulatory care pharmacist can provide the patient the opportunity to seek a second opinion, since this patient is hesitant with receiving one vaccine over the other. Pharmacists can educate other members of the health care community on communication strategies for supporting effective vaccine conversations and motivational interviewing techniques.

(3) **Engaging communities:** Though not as clear-cut, engaging the community in vaccinations can make a large difference in vaccination uptake. In tight-knit communities, everyone talks to each other. In this case, if there was a positive reaction to the vaccine, it may persuade the patient to get her influenza vaccine in the near to distant future.

CONCLUSIONS
Ambulatory care pharmacists represent a key link between...
"The influenza vaccine will give me the flu."

- Influenza vaccines cannot cause influenza illness.
- The influenza vaccine, or flu shot, is manufactured either from an inactivated or killed virus, which is not infectious, or from proteins from the virus that evoke an immune response but does not cause infection.
- Immunity takes up to 2 weeks to ensure adequate antibody protection against the influenza virus; possible exposure to influenza before becoming immunized could explain the seeming relationship between vaccination and the onset of illness.
- Infection with other respiratory illnesses with similar symptoms to influenza or infection with another strain of the influenza virus not contained in the vaccine may explain individuals making this observation.

"It is better to get the flu than to get the influenza vaccine."

- Influenza illness can result in serious infection for high-risk individuals (e.g., young children, adults aged 65 and older, pregnant women, and individuals with underlying medical comorbidities, including asthma, heart disease, diabetes, HIV/AIDS, or cancer).
- Even in otherwise healthy individuals, influenza may be associated with complications that can have serious consequences.
- Preventive measures, such as becoming immunized, carry much lower risks of harm than infection with the influenza virus.

"It is not necessary to receive the influenza vaccine each year, as immunity is long-lasting."

- Immunity against the influenza virus wanes over time, necessitating repeat administration or receipt of an influenza vaccine for each influenza season, even if the upcoming season’s vaccine contains the same strains included in the previous season’s vaccine formulation.
- Additionally, antigenic drift—the small mutations or changes that occur in surface antigens of the virus—necessitates the evaluation and revision of which strains are included in the influenza vaccines each season.

TABLE 2. Resources on Influenza and the Influenza Vaccine for Patients and Health Care Professionals From the Centers for Disease Control and Prevention

| Misconceptions About Seasonal Flu and Flu Vaccines; debunking common patient arguments and theories | https://www.cdc.gov/flu/prevent/misconceptions.htm |
| Flu Vaccine Safety Information; answers to common flu safety questions | https://www.cdc.gov/flu/prevent/general.htm |
| FluSight: Flu Forecasting; a look into what is coming | https://www.cdc.gov/flu/weekly/flusight/index.html |
| Prevent Seasonal Flu; how to keep yourself and others safe | https://www.cdc.gov/flu/prevent/index.html |

It is critical that all pharmacists, regardless of their practice setting or role within the health care system, continue to advocate for vaccinations to reduce illness and promote public health. Influenza vaccination represents an important aspect of such conversations.

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In late 2019, the novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread across the globe, causing the disease known as COVID-19.\(^1\) A pandemic was declared by the World Health Organization (WHO) in March 2020.\(^2\) The CDC speculated that the mitigation measures (e.g., stay-at-home orders, face masks, social distancing, hand cleaning protocols, improved building ventilation, and sharp travel declines) put in place to combat COVID-19 would lead to both a reduction in cases and a global decline in the number of influenza cases during the 2020-2021 season.\(^3\)

**INFLUENZA ACTIVITY**

Influenza viruses typically circulate in the Northern Hemisphere during the winter and spring, but they occasionally can circulate more during the summer months, as did the 2009 H1N1 pandemic strain.\(^4,5\) So far, SARS-CoV-2 has been able to circulate and surge at different times of the year, primarily because new, more contagious variants have been introduced.\(^6\) During the 2020-2021 influenza season, 0.2% of respiratory samples were positive for influenza, whereas positivity reached a peak of 26% to 30% during the prior 3 influenza seasons.\(^3\) During the 2021-2022 season, influenza activity had a bimodal pattern, with a positivity slightly above 6% noted in December 2021; this fell to approximately 2% in January 2022 and peaked again at week 15 of 2022 with 10% positivity.\(^7\) The majority of cases were attributed to type A (H3N2) influenza.

**TYPES OF INFLUENZA VIRUSES**

There are 2 main lineages of human influenza viruses, types A and B.\(^8\) For type A, viruses are subdivided by their major antigenic markers, hemagglutinin and neuraminidase. The currently circulating type A strains include H3N2 (accounting for > 99% of cases), which has been circulating since its introduction in the United States during the 1968 pandemic, and (H1N1)pdm09, the strain from the 2009 pandemic.\(^7,9\) Other viral characteristics that determine vaccine composition each year include epidemiologic data (i.e., particular influenza viruses that circulate around the world at different locations and times) and genetic and antigenic changes.\(^10\) The year-to-year genetic mutations that allow influenza to partially evade our antibodies are called **antigenic drift**.\(^11\) This differs from **antigenic shift**, which refers to a major change in viral hemagglutinin or neuraminidase proteins that may lead to lack of immunity among a population and, ultimately, a pandemic.

**INFLUENZA VACCINES AND VACCINATION**

Nine influenza vaccines—1 live-attenuated and 8 inactivated—were available during the 2021-2022 influenza season (Table).\(^12,13\) The FDA licenses influenza vaccines for use in individuals at least 6 months of age; recommendations by the CDC’s Advisory Committee on Immunization Practices are in line with this age limit. All influenza vaccines marketed in the United States are quadrivalent, meaning that they target a type A (H3N2) virus, a type A (H1N1) virus, a type B (Yamagata lineage) virus, and a type B (Victoria lineage) virus.\(^8\) The vaccines can be further described based upon whether they are manufactured using
Egg-based vaccines have been available for the longest amount of time; however, egg adaptation that may occur during the vaccine manufacturing process can result in a vaccine strain not as well matched to the wild-type circulating strain. Newer vaccine development methods involve using cell-culture or recombinant technology to avoid egg adaptation.

The 2 non-egg–based vaccines available are the quadrivalent cell culture-based inactivated influenza vaccine (ccIIV) Flucelvax Quadrivalent and the quadrivalent recombinant influenza vaccine (RIV) Flublok Quadrivalent.

All influenza vaccines in the United States contain the same major type A and B strains; however, they may differ slightly based on the technology used to manufacture them.

The following are key changes to the ACIP recommendations for influenza vaccines in the 2021-2022 season:

- Flucelvax Quadrivalent is now approved for those aged 2 years and older (previously indicated in those aged ≥ 4 years).
- Influenza vaccines can be coadministered with all other vaccines, including COVID-19 vaccines.
- Vaccination can occur as soon as a recommended vaccine is available for women in their third trimester of pregnancy or children needing 2 doses.

A severe allergic reaction (eg, anaphylaxis) to any ccIIV or RIV or any egg-based vaccine (inactivated influenza vaccine [IIV], live attenuated influenza vaccine [LAIV], or RIV) is a precaution for the use of a quadrivalent IIV or LAIV. A severe allergic reaction to any ccIIV or RIV (including quadrivalent formulations) is a precaution for the use of a quadrivalent ccIIV or RIV.

In March 2022, the FDA voted to approve the 2022-2023 influenza vaccine composition. All influenza vaccines available in the United States remain quadrivalent, offering protection against 4 flu viruses. Although there was no change from the 2021-2022 season for the H3N2 and B/Yamagata component, the H1N1 and B/Victoria strains were changed for the upcoming 2022-2023 season.

The following strains are to be included in influenza vaccines for the 2022-2023 season:

- influenza A (H3N2): A/Darwin/9/2021 (H3N2)-like (egg based) or A/Darwin/6/2021 (H3N2)-like (cell or recombinant based);
- influenza A (H1N1): A/Victoria/2570/2019 (H1N1)pdm09-like virus (egg based) or the A/Wisconsin/588/2019 (H1N1)pdm09-like virus (cell or recombinant based);

---

**TABLE. Available Influenza Vaccines for the 2021-2022 Season**

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Brand</th>
<th>Indicated age</th>
<th>Egg-based technology?</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIV4, standard dose</td>
<td>Afluria Quadrivalent</td>
<td>≥ 6 mo</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Fluarix Quadrivalent</td>
<td>≥ 6 mo</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>FluLaval Quadrivalent</td>
<td>≥ 6 mo</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Fluzone Quadrivalent</td>
<td>≥ 6 mo</td>
<td>X</td>
</tr>
<tr>
<td>HD-IIV4, high dose</td>
<td>Fluzone High-Dose Quadrivalent</td>
<td>≥ 65 y</td>
<td>X</td>
</tr>
<tr>
<td>aIIV4, standard dose</td>
<td>Flud Quadrivalent</td>
<td>≥ 65 y</td>
<td>X</td>
</tr>
<tr>
<td>ccIIV4, standard dose</td>
<td>Flucelvax Quadrivalent</td>
<td>≥ 2 y</td>
<td>X</td>
</tr>
<tr>
<td>RIV4</td>
<td>Flublok Quadrivalent</td>
<td>≥ 18 y</td>
<td>X</td>
</tr>
<tr>
<td>LAIV4</td>
<td>FluMist Quadrivalent</td>
<td>2-49 y</td>
<td>X</td>
</tr>
</tbody>
</table>

aIIV4, adjuvanted inactive influenza vaccine, quadrivalent; ccIIV4, cell culture-based inactive influenza vaccine, quadrivalent; IIV4, inactivated influenza vaccine, quadrivalent; LAIV4, live attenuated influenza vaccine, quadrivalent; mo, month(s); RIV4, recombinant influenza vaccine, quadrivalent; y, year(s).

*Please refer to manufacturer’s package labeling for specific information on various formulations available.

*aFluzone Quadrivalent is currently approved for ages 6 months through 35 months at either 0.25 mL or 0.5 mL per dose; however, 0.25-mL prefilled syringes are not expected to be available for the 2021-2022 influenza season. If a prefilled syringe of Fluzone Quadrivalent is used for a child in this age group, the dose volume will be 0.5 mL per dose.*
Don’t let influenza spread like wildfire. Help contain it with better protection.

Flublok Quadrivalent and Fluzone High-Dose Quadrivalent are vaccines indicated for active immunization against disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Flublok Quadrivalent is approved for use in persons 18 years of age and older. Fluzone High-Dose Quadrivalent is approved for use in persons 65 years of age and older.

Select Important Safety Information

Flublok Quadrivalent and Fluzone High-Dose Quadrivalent should not be given to anyone who has had a severe allergic reaction to any component of the vaccine (including eggs or egg products for Fluzone High-Dose Quadrivalent) or after previous dose of the vaccine. In addition, Fluzone High-Dose Quadrivalent should not be given to anyone who has had a severe allergic reaction after previous dose of any influenza vaccine.

Only 2 influenza vaccines have been proven to prevent more cases of influenza versus standard-dose vaccine comparators in older adults

Fluzone® High-Dose Quadrivalent (Influenza Vaccine)

With 4-strain protection, Fluzone High-Dose Quadrivalent builds on the legacy of the trivalent formulation, which was proven to provide

24% BETTER PROTECTION AGAINST INFLUENZA
(95% CI: 10-37)
due to any lab-confirmed circulating strain compared with standard-dose Fluzone (Influenza Vaccine) in patients 65+,1,3

Based on data from the trivalent formulation, solicited injection site reactions and systemic adverse reactions were slightly more frequent after vaccination with the trivalent formulation compared with a standard-dose vaccine.1

Flublok® Quadrivalent (Influenza Vaccine)

According to a head-to-head randomized controlled efficacy trial among adults 50+, Flublok Quadrivalent was proven to provide

30% BETTER PROTECTION AGAINST INFLUENZA
(95% CI: 10-47)
due to any PCR-conﬁrmed circulating strain versus a standard-dose quadrivalent inactivated influenza vaccine.2,4

In this randomized controlled trial, the most common local and systemic adverse reactions to Flublok Quadrivalent included pain at the injection site, headache, and fatigue.2

Please see Brief Summary of Prescribing Information for Flublok Quadrivalent on the second spread, and for Fluzone High-Dose Quadrivalent please see the third spread.
Important Safety Information for Flublok® Quadrivalent (Influenza Vaccine) and Fluzone® High-Dose Quadrivalent (Influenza Vaccine)

Flublok Quadrivalent and Fluzone High-Dose Quadrivalent should not be given to anyone who has had a severe allergic reaction to any component of the vaccine (including eggs or egg products for Fluzone High-Dose Quadrivalent) or after previous dose of the vaccine. In addition, Fluzone High-Dose Quadrivalent should not be given to anyone who has had a severe allergic reaction after previous dose of any influenza vaccine.

Tell your health care provider if you have ever had Guillain-Barré syndrome (severe muscle weakness) after a previous influenza vaccination.

If Flublok Quadrivalent and Fluzone High-Dose Quadrivalent are given to people with a compromised immune system, including those receiving therapies that suppress the immune system, the immune response may be lower than expected.

Vaccination with Flublok Quadrivalent and Fluzone High-Dose Quadrivalent may not protect all people who receive the vaccine.

For Flublok Quadrivalent, in adults 18 through 49 years of age, the most common side effects were tenderness, and/or pain where you got the shot; headache, tiredness, muscle aches, and joint pain. In adults 50 years of age and older the most common side effects were tenderness, and/or pain where you got the shot; headache, and tiredness.

For Fluzone High-Dose Quadrivalent, in adults 65 years of age and older, the most common side effects were pain, redness, and/or swelling where you got the shot; muscle aches, headache, and general discomfort.

For Flublok Quadrivalent and Fluzone High-Dose Quadrivalent, other side effects may occur.

Please see Brief Summary of Prescribing Information for Flublok Quadrivalent on the second spread, and for Fluzone High-Dose Quadrivalent please see the third spread.

To order Fluzone High-Dose Quadrivalent or Flublok Quadrivalent vaccine, go to VaxServe.com or call 1-800-752-9338.


Learn more at sanofiflu.com
1 INDICATIONS AND USAGE
Flublok Quadrivalent is a vaccine indicated for active immunization against disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Flublok Quadrivalent is approved for use in persons 18 years of age and older [see Clinical Studies (14) in the full prescribing information].

2 DOSAGE AND ADMINISTRATION
For intramuscular injection only.

2.1 Dosage
Administer Flublok Quadrivalent as a single 0.5 mL dose.

2.2 Administration
Invert the prefilled syringe containing Flublok Quadrivalent gently prior to affixing the appropriate size needle for intramuscular administration. Paracetamol drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered. The preferred site for injection is the deltoid muscle. Flublok Quadrivalent should not be mixed in the same syringe with any other vaccine.

4 CONTRAINDICATIONS
Flublok Quadrivalent is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine [see Postmarketing Experience (6.2) and Description (11) in the full prescribing information].

5 WARNINGS AND PRECAUTIONS
5.1 Managing Allergic Reactions
Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

5.2 Guillain Barré Syndrome
The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré Syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than one additional case per 1 million persons vaccinated. If GBS has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of the potential benefits and risks.

5.3 Altered Immunocompetence
If Flublok Quadrivalent is administered to immunocompromised individuals, including persons receiving immunosuppressive therapy, the immune response may be diminished.

5.4 Limitations of Vaccine Effectiveness
Vaccination with Flublok Quadrivalent may not protect all vaccine recipients.

6 ADVERSE REACTIONS
In adults 18 through 49 years of age, the most common (≥10%) injection-site reactions were tenderness (48%) and pain (37%); the most common (≥10%) solicited systemic adverse reactions were headache (20%), fatigue (17%), myalgia (13%), and arthralgia (10%) [see Clinical Trials Experience (6.1)]. In adults 50 years of age and older, the most common (≥10%) injection site reactions were tenderness (34%) and pain (19%); the most common (≥10%) solicited systemic adverse reactions were headache (13%) and fatigue (12%) [see Clinical Trials Experience (6.1)].

6.1 Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a vaccine cannot be directly compared to rates in the clinical studies of another vaccine and may not reflect the rates observed in clinical practice.

Flublok Quadrivalent
Flublok Quadrivalent has been administered to and safety data collected from 998 adults 18-49 years of age (Study 1) and 4328 adults 50 years of age and older (Study 2).

In Studies 1 and 2, local (injection site) and systemic adverse reactions were solicited with the use of a memory aid for 7 days following vaccination, unsolicited adverse events were collected for ~28 days post-vaccination, and serious adverse events (SAEs) were collected for 6 months post-vaccination via clinic visit or remote contact.

Study 1 included 1330 subjects 18 through 49 years of age for safety analysis, randomized to receive Flublok Quadrivalent (n=998) or a comparator inactivated influenza vaccine (Fluarix Quadrivalent, manufactured by GlaxoSmithKline) (n=332) [see Clinical Studies (14) in the full prescribing information]. The mean age of participants was 33.5 years. Overall, 65% of subjects were female, 59% white/Caucasian, 37% black/African American, 15% Native Hawaiian/Pacific Islander, 0.8% American Indian/Alaskan Native, 0.5% Asian, 1.4% other racial groups, and 16% of Hispanic/Latino ethnicity. Table 1 summarizes the incidence of solicited local and systemic adverse reactions reported within seven days of vaccination with Flublok Quadrivalent or the comparator vaccine.

Table 1: Frequency of Solicited Local Injection Site Reactions and Systemic Adverse Reactions within 7 Days of Administration of Flublok Quadrivalent or Comparator in Adults 18-49 Years of Age, Study 1 (Reactogenicity Populations)*

<table>
<thead>
<tr>
<th>Reactogenicity Term</th>
<th>Flublok Quadrivalent</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Subjects with ≥1 injection site reaction†</td>
<td>41%</td>
<td>10%</td>
</tr>
<tr>
<td>Local Tenderness</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Local Pain</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Firmness / Swelling</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Redness</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Subjects with ≥1 systemic reaction‡</td>
<td>12%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>20%</td>
<td>21%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Joint Pain</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Shivering / Chills</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Fever‡</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

NOTE: Data based on the most severe response reported by subjects. Results ≥1% reported to nearest whole percent; results >0 but <1% reported as <1%.

*Comparator = U.S.-licensed comparator quadrivalent inactivated influenza vaccine manufactured by GlaxoSmithKline.
†Study 1 is registered as NCT02290509 under the National Clinical Trials registry.
‡Denominators for fever: Flublok Quadrivalent n = 990, Comparator n = 327.

Flublok Quadrivalent
Flublok Quadrivalent was a vaccine indicated for active immunization against disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Flublok Quadrivalent is approved for use in persons 18 years of age and older [see Clinical Studies (14) in the full prescribing information]. The mean age of participants was 62.7 years. Overall, 58% of subjects were female, 80% white/Caucasian, 18% black/African American, 0.9% American Indian/Alaskan Native, 0.4% Asian, 0.2% Native Hawaiian/Pacific Islander, 0.7% other racial groups, and 5% of Hispanic/Latino ethnicity. Table 2 summarizes the incidence of solicited local and systemic adverse reactions reported within seven days of vaccination with Flublok Quadrivalent or Comparator.

Table 2: Frequency of Solicited Local Injection Site Reactions and Systemic Adverse Reactions within 7 Days of Administration of Flublok Quadrivalent or Comparator in Adults 50 Years of Age and Older, Study 2 (Reactogenicity Populations)*

<table>
<thead>
<tr>
<th>Reactogenicity Term</th>
<th>Flublok Quadrivalent</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Subjects with ≥1 injection site reaction†</td>
<td>38%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

NOTE: Data based on the most severe response reported by subjects. Results ≥1% reported to nearest whole percent; results >0 but <1% reported as <1%.

*Comparator = U.S.-licensed comparator quadrivalent inactivated influenza vaccine manufactured by GlaxoSmithKline.
†Study 2 included 8672 subjects 50 years of age and older for safety analysis, randomized to receive Flublok Quadrivalent (n=4328) or Comparator (Fluarix Quadrivalent, manufactured by GlaxoSmithKline) as an active control (n=4344) [see Clinical Studies (14) in the full prescribing information]. The mean age of participants was 62.7 years. Overall, 58% of subjects were female, 80% white/Caucasian, 18% black/African American, 0.9% American Indian/Alaskan Native, 0.4% Asian, 0.2% Native Hawaiian/Pacific Islander, 0.7% other racial groups, and 5% of Hispanic/Latino ethnicity. Table 2 summarizes the incidence of solicited local and systemic adverse reactions reported within seven days of vaccination with Flublok Quadrivalent or Comparator.
groups, and most events were mild to moderate in severity. ≥ Adverse events occurred in 10.3% of Flublok Quadrivalent and 10.5% of Comparator considered related to study vaccine. Deaths were reported. SAEs were reported by 12 subjects, 10 (1%) Flublok recipients and 2 Comparator recipients. One SAE (pneumonitis) in a Flublok recipient was assessed as possibly related to the vaccine. Among 972 adults 50-64 years of age (Studies 4 and 6 pooled), through up to 6 months post-vaccination, no deaths occurred, and SAEs were reported by 10 subjects, 6 Flublok recipients and 4 Comparator recipients. One of the SAEs, vasovagal syncope following injection of Flublok, was considered related to administration of study vaccine. Among 1078 adults 65 years of age and older (Studies 5 and 6 pooled), through up to 6 months post-vaccination, 4 deaths occurred, 2 in Flublok recipients and 2 in Comparator recipients. None were considered related to the study vaccines. SAEs were reported by 80 subjects (37 Flublok recipients, 43 Comparator recipients). None were considered related to the study vaccines. Among 1314 adults 50 years of age and older (Study 7) for whom the incidence of rash, urticaria, swelling, non-pitting edema, or other potential hypersensitivity reactions were actively solicited for 30 days following vaccination, a total of 2.4% of Flublok recipients and 1.6% of Comparator recipients reported such events over the 30 day follow-up period. A total of 1.9% and 0.9% of Flublok and Comparator recipients, respectively, reported these events in the 7 days following vaccination. Of these solicited events, rash was most frequently reported (Flublok 1.3%, Comparator 0.8%) over the 30 day follow-up period.

### Drug Interactions

Data evaluating the concomitant administration of Flublok Quadrivalent with other vaccines are not available.

### USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Pregnancy Exposure**

Pregnancy outcomes in women who have been exposed to Flublok Quadrivalent during pregnancy are being monitored. Sanofi Pasteur Inc. is maintaining a prospective pregnancy exposure registry to collect data on pregnancy outcomes and newborn health status following vaccination with Flublok Quadrivalent during pregnancy. Healthcare providers are encouraged to enroll women who receive Flublok Quadrivalent during pregnancy in Sanofi Pasteur Inc.’s vaccination pregnancy registry by calling 1-800-822-2463.

**Risk Summary**

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the observed background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively. Available data on Flublok Quadrivalent and Flublok (trivalent formulation) administered to pregnant women are insufficient to inform vaccine-associated risks in pregnant women.

There were no developmental studies of Flublok Quadrivalent formulation performed in animals. The developmental effects of Flublok (trivalent formulation) are relevant to Flublok Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions. A developmental study of Flublok (trivalent formulation) has been performed in rats administered 0.5 mL divided of Flublok (trivalent formulation) prior to mating and during gestation. This study revealed no evidence of harm to the fetus due to Flublok (trivalent formulation) [see Data].
Clinical Considerations

525 subjects determine whether elderly subjects respond differently from younger subjects.

Disease-associated Maternal and/or Embryo/Fetal Risk
Pregnant women are at increased risk of complications associated with influenza infection compared to non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data Animal
In a developmental toxicity study, female rats were administered 0.5 mL divided of Flublok (trivalent formulation) by intramuscular injection twice prior to mating (35 days and 14 days prior to mating) and on gestation Day 6. No vaccine-related fetal malformations or variations and no adverse effects on pre-weaning development were observed in the study.

8.2 Lactation
Risk Summary
It is not known whether Flublok Quadrivalent is excreted in human milk. Data are not available to assess the effects of Flublok (trivalent formulation) or Flublok Quadrivalent on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Flublok Quadrivalent and any potential adverse effects on the breastfed child from Flublok Quadrivalent or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

6.4 Pediatric Use
Data from a randomized, controlled trial demonstrated that children 6 months to less than 3 years of age had diminished hemagglutinin inhibition (HI) responses to Flublok (trivalent formulation) as compared to a U.S.-licensed influenza vaccine approved for this age population, strongly suggesting that Flublok (trivalent formulation) would not be effective in children younger than 3 years of age. Safety and effectiveness of Flublok Quadrivalent have not been established in children 3 years to less than 18 years of age.

8.5 Geriatric Use
Data from an efficacy study (Study 2), which included 1759 subjects ≥65 years and 525 subjects ≥75 years who received Flublok Quadrivalent, are insufficient to determine whether elderly subjects respond differently from younger subjects [see Clinical Trials Experience (6.1) and Clinical Studies (14) in the full prescribing information].

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Distributed by Sanofi Pasteur Inc.

Flublok is a registered trademark of Protein Sciences Corporation.

INFB4-BPLR-SL-JUL20 Revised: July 2020

Fluzone High-Dose Quadrivalent
(Influenza Vaccine), Suspension, for intramuscular injection
2020-2021 Formula

Clinical Considerations

INFB4-BPLR-SL-JUL20 Revised: July 2020

B:8.125” T:7.875” S:7”

Clinical Considerations

525 subjects determine whether elderly subjects respond differently from younger subjects.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome
If Guillain-Barré syndrome (GBS) has occurred within 6 weeks following any previous influenza vaccination, the decision to give Fluzone High-Dose Quadrivalent should be based on careful consideration of the potential benefits and risks. The 1976 swine influenza vaccine was associated with an elevated risk of GBS. Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated. GBS has also been temporarily associated with influenza disease. (See references 1 and 2 in the full prescribing information.)

5.2 Preventing and Managing Allergic Reactions
Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

5.3 Altered Immune Competence
If Fluzone High-Dose Quadrivalent is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be lower than expected.

5.4 Limitations of Vaccine Effectiveness
Vaccination with Fluzone High-Dose Quadrivalent may not protect all recipients.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trial(s) of a vaccine cannot be directly compared to rates in the clinical trial(s) of another vaccine and may not reflect the rates observed in practice. One clinical study has evaluated the safety of Fluzone High-Dose Quadrivalent.

Study 1 (NCT03282240, see https://clinicaltrials.gov) was a randomized, active-controlled, modified double-blind pre-licensure trial conducted in the U.S. The study compared the safety and immunogenicity of Fluzone High-Dose Quadrivalent to those of Fluzone High-Dose (trivalent formulation). The safety analysis set included 1777 Fluzone High-Dose Quadrivalent recipients, 443 Fluzone High-Dose recipients, and 450 investigational Fluzone High-Dose containing the alternate B influenza strain recipients.

The most common reactions occurring after Fluzone High-Dose Quadrivalent administration were injection-site pain (41.3%), myalgia (22.7%), headache (14.4%), and malaise (13.2%). Onset usually occurred within the first 3 days after vaccination. The majority of solicited reactions resolved within three days of vaccination. Table 1 displays solicited adverse reactions for Fluzone High-Dose Quadrivalent compared to Fluzone High-Dose reported within 7 days after vaccination and collected using standardized diary cards.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Fluzone® High-Dose Quadrivalent is not approved for use in persons <65 years of age. There are limited human data on Fluzone High-Dose and no animal data available on Fluzone High-Dose Quadrivalent to establish whether there is a vaccine-associated risk with use of Fluzone High-Dose Quadrivalent in pregnancy.

8.2 Lactation
Fluzone High-Dose Quadrivalent is not approved for use in persons <65 years of age. No human or animal data are available to assess the effects of Fluzone High-Dose Quadrivalent on the breastfed infant or on milk production/excretion.

8.4 Pediatric Use
Safety and effectiveness of Fluzone High-Dose Quadrivalent in children younger than 18 years of age have not been established.

8.5 Geriatric Use
Safety, immunogenicity, and efficacy of Fluzone High-Dose Quadrivalent have been evaluated in adults 65 years of age and older [see Adverse Reactions (6.1) and Clinical Studies (14) in the full prescribing information].

Manufactured by: Sanofi Pasteur Inc., Swiftwater PA 18370 USA
INHDQ-BPLR-SL-JUL20 Revised: July 2020

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### Table 1: Study 1: Frequency of Solicited Injection-Site Reactions and Systemic Adverse Events within 7 Days after Vaccination with Fluzone High-Dose Quadrivalent or Fluzone High-Dose, Adults 65 Years of Age and Older

<table>
<thead>
<tr>
<th></th>
<th>Fluzone High-Dose Quadrivalent (N=1761-1768)</th>
<th>Fluzone High-Dose (N=885-889)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade 3</td>
<td>Any Grade 3</td>
</tr>
<tr>
<td><strong>Local Reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>41.3</td>
<td>36.4</td>
</tr>
<tr>
<td>Erythema</td>
<td>6.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Swelling</td>
<td>4.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Induration</td>
<td>3.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Bruising</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Systemic Reactions</strong></td>
<td></td>
<td></td>
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<tr>
<td>Myalgia</td>
<td>22.7</td>
<td>18.9</td>
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<tr>
<td>Headache</td>
<td>14.4</td>
<td>13.6</td>
</tr>
<tr>
<td>Malaise</td>
<td>13.2</td>
<td>13.4</td>
</tr>
<tr>
<td>Shivering</td>
<td>5.4</td>
<td>4.7</td>
</tr>
<tr>
<td>Fever</td>
<td>0.4</td>
<td>0.9</td>
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</table>

*NCT03282240
| N is the number of vaccinated participants with available data for the events listed.
| Safety results for the Fluzone High-Dose and investigational Fluzone High-Dose containing the alternate B influenza strain recipients were pooled for the analysis.
| Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
| Grade 3: > 100 mm
| Grade 3: ≥ 102.1°F (39.0°C)

Based on data from Fluzone High-Dose, solicited injection site reactions and systemic adverse reactions were slightly more frequent after vaccination with Fluzone High-Dose compared to a standard-dose vaccine.

Unsolicited non-serious adverse events were reported in 279 (15.7%) recipients in the Fluzone High-Dose Quadrivalent group and 140 (15.7%) recipients in the Fluzone High-Dose group. The most commonly reported unsolicited adverse event was cough.

Within 180 days post-vaccination, 80 (4.5%) Fluzone High-Dose Quadrivalent recipients and 48 (5.4%) Fluzone High-Dose recipients experienced a serious adverse event (SAE). None of the SAEs were assessed as related to the study vaccines.

6.2 Postmarketing Experience
The following additional adverse events have been spontaneously reported during the postmarketing use of Fluzone High-Dose, Fluzone, or Fluzone Quadrivalent and may occur in people receiving Fluzone High-Dose Quadrivalent. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to Fluzone High-Dose, Fluzone, or Fluzone Quadrivalent.

- **Blood and Lymphatic System Disorders**: Thrombocytopenia, lymphadenopathy
- **Immune System Disorders**: Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- **Eye Disorders**: Ocular hypertension
- **Nervous System Disorders**: Guillain-Barré syndrome (GBS), convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell’s palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia
- **Vascular Disorders**: Vasculitis, vasodilatation
- **Respiratory, Thoracic and Mediastinal Disorders**: Dyspnea, cough, wheezing, throat tightness, oropharyngeal pain, and minor hemorrhage
- **Gastrointestinal Disorders**: Vomiting
- **Skin and Subcutaneous Tissue Disorders**: Stevens-Johnson syndrome
- **General Disorders and Administration Site Conditions**: prunus, asthenia)
- **fatigue, chest pain, chills**
## INFLUENZA VACCINE EFFECTIVENESS

During the COVID-19 pandemic, low influenza activity increased the uncertainty of estimates for the effectiveness of the influenza vaccine.\(^1\) Vaccine effectiveness (VE) is determined through observational studies; however, results from such studies often are influenced by various forms of bias that can make it difficult to interpret outcomes. The US Flu Vaccine Effectiveness Network interim estimates were unable to demonstrate a benefit against mild to moderate influenza in the 2021-2022 season for H3N2, that season’s most commonly circulating strain.

Data on protection against severe disease are not available until after the end of the season. According to the CDC, from 2015 to 2020, VE for influenza vaccines ranged from 29% to 48%.\(^2\) Although there is evidence that the high-dose influenza vaccine\(^3,4\) and adjuvanted influenza vaccine, licensed for individuals aged 65 years and older, led to a better immune and clinical response, season-to-season variation in VE and the need for more comparative data have prevented the CDC from making a preferential recommendation for these vaccines.\(^5-7\)

### ROLE OF PHARMACISTS IN EDUCATING PATIENTS ON INFLUENZA VACCINES

During the 2020-2021 influenza season, the CDC reported that pharmacies surpassed doctor’s offices as the most common place where adults received an influenza vaccine.\(^8\) Perhaps due to fears of acquiring COVID-19 and influenza, the influenza vaccination rate in adults at least 65 years old increased from 70% (2019-2020 season) to 75% (2020-2021 season). However, the pediatric influenza vaccination rate decreased over this time period.

The CDC produced a toolkit for pharmacists to help increase influenza vaccination rates in patients, especially in those with vaccine hesitancy, and to improve vaccine confidence.\(^9\) As the COVID-19 pandemic continues, influenza has not gone away. It will take the efforts of pharmacists and other providers to manage immunization for both diseases this coming autumn.

## REFERENCES


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\(^2\) MMWR. 2021;70(5):1-28. doi:10.15585/mmwr.rr7005a1


Pharmacies and pharmacists are increasingly utilized for point-of-care (POC) services, including testing for infections that can be diagnosed via rapid testing, such as influenza, respiratory syncytial virus (RSV), COVID-19, and group A Streptococcus (group A strep). Our health care system is evolving with greater demand for an expanded access model that includes utilizing the most accessible health care professionals: pharmacists.1

RAPID DIAGNOSTIC TESTING FOR RESPIRATORY ILLNESSES

The use of POC rapid diagnostic testing (RDT) is not new2; however, the global COVID-19 pandemic exacerbated the need for additional testing sites, such as pharmacies, for patients to access these types of tests.3 RDT can quickly identify or rule out a specific pathogen; the results can guide antimicrobial therapy (if appropriate), and aid in decisions regarding infection control measures, such as the need for isolation.4,5 Because rapid diagnostics can markedly reduce the time to pathogen identification and determination of antimicrobial susceptibility (when indicated), they offer providers the ability to optimize pharmacotherapy.4 RDT for influenza became available in the 1990s and gained widespread use due to its ease of use, appropriateness for POC testing, and capability to provide quick results to best utilize therapeutics within 48 hours of symptom onset.2 Now, over-the-counter rapid diagnostic tests for COVID-19 have become widely available and are increasingly being used by the public for quick, at-home testing.5,7

Influenza viruses, RSV, group A strep, and SARS-CoV-2 all are common respiratory tract pathogens that cause a variety of signs and symptoms. The illnesses they cause are often spread through respiratory droplets released during talking, sneezing, or coughing by the infected individual.6,8,9 COVID-19, which is caused by the SARS-CoV-2 virus, and the flu share common symptoms including fever, chills, cough, runny nose, sore throat, or difficulty breathing. Symptoms may vary, and depending on the causative organism, there may be either a rapid or slow onset of symptoms or differences in duration of illness. SARS-CoV-2 infection can also result in specific symptoms such as loss of taste and smell, which are unique and differentiate COVID-19 from other infections.12 Surface transmission can also occur when a person touches an object that has droplets on it and then touches their mouth, nose, or eyes.

The influenza virus infects the nose, throat, and sometimes lungs.9 The most frequent symptoms are fever, chills, cough, sore throat, runny or stuffy nose, muscle or body aches, headache, and fatigue.

RSV affects the breathing passages (ie, nose and throat) and lungs. It is associated with cold-like symptoms, notably runny nose, decreased appetite, coughing, sneezing, fever, and wheezing. Infants, young children, and older adults are particularly susceptible to developing severe RSV infections, such as pneumonia and bronchiolitis (inflammation of the small airways in the lungs).10 Group A strep bacteria live in the nose and throats of infected individuals. The
most common symptoms include sore throat, pain with swallowing, fever, red and swollen tonsils, and swollen lymph nodes.11

COVID-19 can be transmitted from respiratory droplets in the nose or throat of infected individuals; these droplets can linger in the air. Unlike the common cold, which is associated with symptoms that primarily affect the respiratory system and lungs, COVID-19 can also affect other body systems and produce a wide range of symptoms, with illness ranging from mild to severe.12 Symptoms may include fever, chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion and runny nose, nausea, vomiting, and diarrhea.13

Understanding if the infection is caused by a virus or a bacterium is extremely important, especially due to the rise in multidrug-resistant organisms from inappropriate antibiotic usage.14 For example, many pathogens are associated with pharyngitis; however, group A strep bacteria are the only ones that should be treated with an antibiotic.15 Contrast this with influenza, RSV, and COVID-19, which are all caused by viruses and have some similar symptoms but are managed very differently.16−18 The timing of the identification of these organisms also will determine if treatment is indicated. For influenza, antiviral treatment is most effective and ideally administered within 48 hours of onset of illness, although it can still be beneficial if given later.16 With COVID-19 infection, oral antivirals can be administered up to 5 days following symptom onset.18 Currently no specific therapy exists for RSV; however, early identification can ensure that supportive care can be administered quickly.17

### TESTING MODALITIES

It can be helpful to explain to patients the differences among common testing modalities so they understand why some tests are available in a pharmacy setting and others are not. Common testing methodologies are described in Table 1.4,19−22

Because RDT often necessitates the evaluation of a clinical specimen such as blood, stool, or bodily fluids, Clinical Laboratory Improvement Amendment (CLIA)-waived testing requirements must be met for testing to be performed in a pharmacy.4,19,21 Samples are used qualitatively or quantitatively to produce results within 15 minutes to a few hours, depending on the testing modality.4

During the COVID-19 pandemic, the HHS secretary declared a public health emergency and indicated the need to fast-track in vitro diagnostic tests to identify COVID-19 infection.24 Thus, the FDA made some tests available through its Emergency Use Authorization (EUA).25 The FDA may issue EUA status to a product when specific criteria are met. This includes times when there are no adequate, approved, or available alternatives, and the overall scientific evidence suggests that the product may be effective in

<table>
<thead>
<tr>
<th>TABLE 1. Types of Diagnostic Techniques for Pathogens4,19-22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Antigen (antibody-antigen)</td>
</tr>
<tr>
<td>PCR; NAAT (RT-PCR for RNA)</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; NAAT, nucleic acid amplification; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; RT-PCR, reverse-transcriptase PCR.

aA limitation of these assays is that patients may test positive for these antigens even if they have already recovered from an infection.
Diagnostic testing for COVID-19 given EUA have not undergone the same type of review as an FDA-approved or -cleared test. The use of these products is in effect only during the emergency declaration and will be terminated after it expires if full FDA clearance or approval is not obtained.

There are several types of testing methods to diagnose and, in some cases, rule out infection with the influenza virus, SARS-CoV-2, and RSV. Table 2 and Table 3 provide more detailed information about these tests.

An abundance of innovation arose out of necessity to accurately diagnose COVID-19. The use of unique tests, such as the CLIA-waived POC tests from Abbott (ID NOW), has been a game changer for many practices. These products can detect SARS-CoV-2, the influenza virus, and RSV. Details regarding the ID NOW testing platform are provided in Table 3.

Quality control (QC) is extremely important when conducting POC testing. Proper procedures must be followed to ensure the accuracy of results. Multiple steps must be considered, including how the sample is collected, stored,
and handled post collection. Proper handling of samples includes aseptic techniques and the use of personal protective equipment, including clean gloves. Further, it is important to control the temperature of the laboratory samples and testing solutions. Most are required to be at room temperature before testing can be performed. Positive and negative controls should be tested using the QC test instructions included with the platform. QC results are generated as pass or fail. If the QC test fails, no further testing should be performed using that device.

CONCLUSIONS

CLIA-waived POC testing is a value-added service that can expand the scope of practice for many community pharmacies. This needed and valuable service to the community can directly impact public health by decreasing the incidence of communicable disease. The early identification, treatment, and management of infectious diseases such as influenza, RSV, group A strep, and COVID-19 can have major societal implications, such as reducing lost work days and productivity. Results from RDT facilitate proper therapeutic management and reduce inappropriate antibiotic utilization. The COVID-19 pandemic has shown us that these types of services can be easily incorporated into the pharmacy setting with some purposeful planning and training. In addition, among the newest platforms are those that have made testing even easier by using a single device to detect multiple organisms via molecular testing. If these types of services were offered in even half of all pharmacy settings, the impact would be tremendous. Increased health and wellness of our communities is possible through these innovative solutions. ■

REFERENCES

*streptococcus pneumoniae* is an infectious pathogen associated with considerable morbidity and mortality. It is a gram-positive, anaerobic organism that has more than 100 documented serotypes. 

* S pneumoniae is the most common pathogen responsible for the development of pneumonia, and it is also associated with other infections (eg, otitis, sinusitis).

Between 2018 and 2019, the incidence of invasive pneumococcal disease (IPD) was 24 cases per 100,000 in patients aged 65 years and older. IPD can present as pneumonia, meningitis, or bacteremia.

Adults who are at least 65 years old and those with certain immunocompromising conditions are at increased risk of developing IPD. In children younger than 2 years, *S pneumoniae* accounts for 25% to 30% of pneumonia cases and 40% of bacteremia cases. In children younger than 5 years, it is the leading cause of bacterial meningitis.

Routine pneumococcal vaccination is associated with a marked reduction in the rate of *S pneumoniae* infections. Capsular polysaccharides on the surface of pneumococci play a key role in the pathogenicity of *S pneumoniae*; they and are used to classify serotypes. The first pneumococcal polysaccharide vaccine (PPSV) was licensed in the United States in 1977, and it covered 14 serotypes. The current pneumococcal polysaccharide vaccine (PPSV23) was approved in 1983 as a replacement for the 14-valent vaccine; it covers 23 serotypes. The antibody response to PPSV23 has shown to be poor in children younger than 2 years due to the immaturity of the infant immune system; therefore, its use is not recommended in this age group. Pneumococcal conjugate vaccines (PCV) join serotypes to a nontoxic variant of the diphtheria toxin. The first PCV, approved in 2000, covered 7 serotypes (PCV7). In 2010, PCV7 was replaced with the 13-valent vaccine, PCV13.

From 2018 to 2019, the 13 serotypes represented in the PCV13 were responsible for 27% of IPD cases in adults aged 65 years and older, whereas additional serotypes unique to PPSV23 accounted for 35% of IPD cases.

In adults aged 19 to 64 years with underlying conditions, the serotypes in the PCV13 accounted for 30% of IPD cases, whereas additional serotypes unique to PPSV23 accounted for 43% of cases.

In 2021, two additional PCVs were approved: PCV15 and PCV20. The addition of serotypes unique to PCV15 and PCV20 should improve protection from IPD in adults aged 65 years and older and in those aged 19 to 64 years with underlying conditions. This protective advantage coupled with associated cost savings in patients at least 65 years of age led the Advisory Committee on Immunization Practices (ACIP) at the CDC to recommended PCV15 or PCV20 instead of PCV13 in these populations.

**COMPOSITION OF PCV15 AND PCV20**

PCV15 and PCV20 are single-dose vaccinations. Both are indicated for the prevention of pneumonia and IPD caused by *S pneumoniae*. PCV15, available as the brand name product Vaxneuvance (Merck Sharp & Dohme Corp), is a preservative-free sterile suspension of purified capsular polysaccharides from 15 *S pneumoniae* serotypes. The vaccine also contains a genetically detoxified diphtheria toxin,
Corynebacterium diphtheriae CRM₁₉₇ protein, as a carrier protein. It is indicated for use in individuals 6 weeks of age and older. PCV20, available as brand name Prevnar 20 (Wyeth Pharmaceuticals LLC), also is a sterile suspension that contains saccharides of the capsular antigens from 20 S pneumoniae serotypes along with a CRM₁₉₇ carrier protein. It is indicated for use in adults (aged ≥ 18 years).

When compared with PCV13, PCV15 contains 2 additional serotypes that account for about 15% of IPD cases in adults aged 65 years and older. Similarly, when compared with PCV13, PCV20 contains 7 more unique serotypes that are associated with approximately 27% of IPD cases. PCV20 contains 3 fewer serotypes than does PPSV23; however, PCVs generally induce a more robust immune response as compared with the transient protection provided by PPSV23. Details regarding specific serotype composition can be found in the Table 1.

Efficacy of PCV15 and PCV20
The FDA approval of these 2 vaccines was based on findings from randomized controlled trials comparing antibody responses after administration of the preexisting PCV13 and PPSV23. Studies evaluated the immunogenicity of PCV15 compared with that of PCV13 in various populations, including healthy adults aged at least 50 years, adults aged 18 to 49 years at increased risk for pneumococcal disease (including Native Americans, who are at higher risk of IPD than the general population), and adults aged at least 18 years with HIV infection. Results from these studies demonstrated comparable or higher antibody responses with PCV15 than with PCV13 among the shared serotypes.

Individuals who receive PCV13 or PCV15 should receive a dose of PPSV23; generally, it is given 1 year later. PPSV23 offers additional coverage against serotypes that can cause IPD. In studies in which patients received PCV13 or PCV15 followed by PPSV23, those receiving PCV15 demonstrated immune responses for all 15 serotypes, and immunogenicity was comparable among the shared serotypes with PCV13. Studies evaluating PCV20 versus PCV13 showed comparable immune responses for all shared serotypes, with PCV20 being associated with a slightly lower percentage of seroresponders for 2 serotypes. In studies comparing PCV20 with PPSV23, those administered PCV20 had numerically higher antibody titers and a greater percentage of seroresponders to the majority of shared non-PCV13 serotypes.

Economic models assessing the cost-effectiveness of PCV15 or PCV20 followed by PPSV23 in adults aged 65 years and older determined cost savings. These findings of similar immunogenicity coupled with comparable safety profiles and potential cost savings led to the current ACIP pneumococcal vaccine recommendations of PCV15 and PCV20 for adults aged at least 65 years and those aged 19 to 64 years with certain underlying medical conditions or risk factors.

Table 1. Pneumococcal Vaccine Serotypes

<table>
<thead>
<tr>
<th>Serotypes</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6A</th>
<th>6B</th>
<th>7F</th>
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<th>19F</th>
<th>20</th>
<th>22F</th>
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<th>33F</th>
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<tbody>
<tr>
<td>PCV13</td>
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<td>PPSV23</td>
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PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine.

2022 ACIP Recommendations
The ACIP recommends PCV15 or PCV20 for PCV-naïve adults who are aged 65 years or older and those aged 19 to 64 years who have certain underlying conditions or risk factors (eg, immunocompromising conditions, alcoholism, lung disease). If PCV15 is used, a dose of PPSV23 should be administered at least 1 year later. A minimum interval of 8 weeks can be considered for adults with a cochlear implant, cerebrospinal fluid leak, or immunocompromising conditions (eg, chronic renal failure, nephritic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, HIV, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplant,
congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies). Pneumococcal vaccine recommendations for adults based on different clinical scenarios are outlined in the Table 2.³

In pediatric patients, a 3-dose primary series of PCV13 is recommended as routine vaccination at 2 months, 4 months, and 6 months of age; a booster dose is recommended at 12 to 15 months of age. The ACIP recommends that children aged 6 to 18 years who have certain medical conditions and have not received a pneumococcal vaccine be given 1 dose of PCV13 followed 8 weeks later by 1 dose of PPSV23. A second dose of PPSV23 is recommended 5 years after the first dose for children with anatomic or functional asplenia, HIV infection, or other immuno-compromising conditions. Children aged 6 to 18 years who already received 1 dose of PPSV23 should be given 1 dose of PCV13 eight weeks after the last PPSV23 dose.¹⁶

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Vaccine Schedule</th>
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<tbody>
<tr>
<td>Adults aged ≥ 65 y who have not previously received a PCV or whose previous vaccination history is unknown</td>
<td>PCV20, or PCV15 followed by PPSV23</td>
</tr>
<tr>
<td>Adults aged 19-64 y with underlying conditions or other risk factors* who have not received a PCV or whose previous vaccination history is unknown</td>
<td>PCV20, or PCV15 followed by PPSV23</td>
</tr>
<tr>
<td>Adults who have already received PPSV23 only</td>
<td>PCV20 or PCV15 at least 1 y after their last PPSV23 dose &gt;If PCV15 is used, it does not need to be followed by another dose of PPSV23</td>
</tr>
<tr>
<td>Adults who have already received PCV13 alone*</td>
<td>Complete pneumococcal vaccine series with 1 dose of PPSV23 or PCV20 (if PPSV23 is unavailable)</td>
</tr>
<tr>
<td>Adults who have already completed the pneumococcal series with PCV13 and PPSV23*</td>
<td>Patients and providers should await further guidance from the CDC and ACIP regarding the recommended course of action.</td>
</tr>
</tbody>
</table>

ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; y, year(s).

*Alcoholism; chronic heart, liver, or lung disease; chronic renal failure; cigarette smoking; cochlear implant; congenital or acquired asplenia; cerebrospinal fluid leak; diabetes mellitus; generalized malignancy; HIV; Hodgkin disease; immunodeficiency; iatrogenic immunosuppression; leukemia, lymphoma, or multiple myeloma; nephrotic syndrome; solid organ transplant; sickle cell disease; or other hemoglobinopathies.

³At this time, there is limited guidance regarding the use of PCV15 or PCV20 in patients who already received PCV13 or PCV13 and PPSV23.

TABLE 2. Pneumococcal Vaccine Recommendations for Adults Based on Patient Demographics³

once they are published in the Morbidity and Mortality Weekly Report.

ADMINISTRATION AND STORAGE OF PCV15 AND PCV20

PCV15 and PCV20 are supplied in 0.5-mL prefilled syringes. Both vaccines are delivered intramuscularly as a single dose. Prior to administration, the syringe should be held horizontally and shaken vigorously until the suspension inside appears homogeneous. In the event that the vaccine cannot be resuspended, or if discoloration or particulate matter is observed, the vaccine should not be used.⁶,⁷

Vaccines should be stored in the refrigerator at temperatures of 36 °F to 46 °F and should not be frozen.⁶,⁷ Storage of syringes horizontally may minimize resuspension time. PCV15 must be protected from light.⁶

SAFETY OF PCV15 AND PCV20

Adverse events (AEs) associated with the use of PCV15 and PCV20 are similar and include injection-site pain, swelling, erythema, fatigue, muscle pain, joint pain, and headache.⁶,⁷ Contraindications to these vaccines include severe allergic reaction (eg, anaphylaxis) to any component of PCV20 or PCV15 or to diphtheria toxoid. Safety and immunogenicity data on PCV20 are not available for immunocompromised individuals, and vaccination should be considered on an
individual basis. Any AEs noted from these vaccinations should be reported to the Vaccine Adverse Event Reporting System (https://vaers.hhs.gov).6,7

COUNSELING POINTS
Prior to administering pneumococcal vaccines, patients should be educated about potential AEs associated with these vaccinations. Recipients also should be given the Vaccine Information Statement that is available on the CDC website (https://www.cdc.gov/vaccines/hcp/vis/current-vis.html); it contains information about the vaccine’s purpose, indication, possible AEs, and other safety considerations.2

CONCLUSIONS
S pneumoniae may cause IPD, which can lead to hospitalization and death. PCV13 and PPSV23 have reduced IPD in both the pediatric and adult population. The use of PCV20 alone or PCV15 with PPSV23 should continue to reduce both invasive and noninvasive disease in patients. Pharmacists are in an excellent position to educate and counsel patients on current recommendations. They also can play a role in vaccine advocacy and help patients overcome barriers related to vaccination. ■

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