CONNECTICUT MEDICAL ASSISTANCE PROGRAM DEPARTMENT OF SOCIAL SERVICES & HEALTH INFORMATION DESIGNS

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"The burden of influenza disease in the United States can vary widely and is determined by a number of factors including the characteristics of circulating viruses, the timing of the season, how well the vaccine is working to protect against illness, and how many people got vaccinated. While the impact of flu varies, it places a substantial burden on the health of people in the United States each year. The CDC (Centers for Disease Control) estimates that influenza in the United States has resulted in between 9.3 million – 49.0 million illnesses, between 140,000 – 960,000 hospitalizations and between 12,000 – 79,000 deaths annually since 2010.[1]"

Influenza viruses circulate in the U.S. typically from late fall through early spring. From October 2017 through April 2018, the CDC estimates that the influenza-related hospitalization rate was 106.6 per 100,000 population, with the highest rates occurring in children 0-4 years of age, adults 50-64 years of age, and adults >65 years of age being the highest. Complicating chronic conditions such as heart or lung disease, obesity, or diabetes occurred in more than 90% of hospitalized adults indicating that chronic underlying disease plays a role in contributing to the complications associated with influenza.[2] 171 pediatric deaths occurred during the 2017-2018 season in the U.S. and more than 75% of these children were not vaccinated.[2] It has been estimated that less than 50% of people in high risk categories receive the flu vaccine each year.[3]

During the 2017-2018 influenza season in Connecticut, 59,642 patients enrolled in the Connecticut Medical Assistance Program (approximately 8% of the Medicaid population) received an influenza vaccine through a pharmacy or their doctor's office. Additionally, 27,521 patients enrolled in the Connecticut Medical Assistance Program (approximately 3.7% of the Medicaid population) received a diagnosis of influenza during the 2017-2018 influenza season .

Transmission of influenza occurs via person to person by direct contact with virus particles from the infected person coughing or sneezing, or by indirect contact with respiratory secretions on contaminated surfaces and then touching the eyes, nose, or mouth.

Signs and Symptoms of influenza can include: abrupt onset of fever, chills, myalgia, sore throat, nonproductive cough, headache, and rhinorrhea. Complications of influenza can include: pneumonia, myocarditis, and worsening of underlying chronic pulmonary disorders. Influenza can cause serious illness, hospitalization, and death. Groups with the highest risk of complications include older adults, very young children, pregnant women, and those with chronic underlying medical conditions.[4]

Each year, to help combat influenza, the Advisory Committee on Immunization Practices (ACIP) creates recommendations regarding the use of seasonal influenza vaccines within the United States. Recommendations regarding the prevention and control of seasonal influenza for the 2018-19 influenza season were published in the Centers for Disease Control (CDC) Morbidity and Mortality Weekly Report (MMWR) during the summer of 2018 and include four important points below[5]:

1. Changes to the composition of the vaccines for the 2018-2019 season (includes both trivalent and quadrivalent formulations)
2. Recommendations for the use of LAIV4 (Live Attenuated Influenza Vaccine) can now be used in age appropriate categories when appropriate (the previous two influenza seasons recommended against its use due to observational data indicating that LAIV was poorly effective against certain influenza A strains)
3. Patients with a history of egg allergy of any sensitivity may receive any licensed, recommended, and age appropriate influenza vaccine
4. Recent regulatory actions, including expansion of the age indication for Afluria Quadrivalent (IIV4) from ≥18 years to ≥5 years and for Fluarix Quadrivalent from ≥3 years to ≥6 months

The ACIP recommends that vaccinations are to occur by the end of October but can continue to be offered as long as the virus is in circulation.[5] Additionally, it is recommended that the following groups are to receive the influenza vaccination during the 2018-19 season[5]:

- Routine annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications
- A licensed, age appropriate influenza vaccine should be used
- Emphasis should be placed on vaccination of high-risk groups and their contacts/ caregivers. When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to:
- Children aged 6-59 months
- Adults aged ≥50 years
- Persons with chronic pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)
- Persons who are immunocompromised due to any cause
- Women who are or will be pregnant during the influenza season

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- Children and adolescents (aged 6 months through 18 years) receiving aspirin or salicylate containing medications and who might be at risk for Reye Syndrome
- Residents of nursing homes and other long term care facilities
- American Indians/Alaska Natives
- Persons who are extremely obese (BMI ≥ 40)
- Caregivers and contacts of those at risk (healthcare personnel, household contacts and caregivers of children ≤ 59 months, and household contacts and caregivers of persons with medical conditions that put them at risk of severe complications)

There are 3 basic types of influenza: A, B, and C. Influenza A causes the most severe illness and can affect both humans and animals (birds, pigs, horses).[6] Influenza type A has subtypes that are determined, and named, by the surface antigens hemagglutinin (H) and neuraminidase (N). There are three types of hemagglutinin in humans (H1, H2, and H3) that have a role in virus attachment to cells. There are two types of neuraminidase (N1 and N2) that have a role in virus penetration into cells.[3] Influenza B only affects humans and is milder compared to A. Influenza C only affects humans and rarely causes illness. C is not associated with epidemics and not included in vaccine formulation.

All 2018-2019 seasonal influenza vaccines contain two A strains and one B strain; an influenza A(H1N1) strain, an influenza A (H3N2) strain, and an influenza B (Victoria lineage) strain.[7] Prior to the 2013-14 influenza season, only trivalent influenza vaccines that included two A strains and a single B strain were available. Since the 2013-14 season, however, quadrivalent influenza vaccines that include two A strains and two B strains have been formulated.[7] Quadrivalent vaccines are formulated to provide more protection against the less common influenza B viruses. Two antigenically distinct lineages (Victoria and Yamagata) of influenza B viruses have been in circulation globally since the 1980's. Historically, it has been difficult to determine which B lineage will predominate during each influenza season so, in theory, providing patients with a quadrivalent vaccine may provide additional coverage against both B lineages since covering only one B lineage provides minimal cross protection against the other.[7]

Nomenclature exists to help with the naming of individual viruses. (1) virus type, (2) geographic origin, (3) strain number, (4) year of isolation, (5) virus subtype. The strains that are covered in this year's influenza vaccine in the U.S. are listed below.

Trivalent vaccines for the 2018-2019 vaccine will contain[5]:

- A/Michigan/45/2015 (H1N1)pdm09-like virus
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus
- B/Colorado/06/2017-like virus (Victoria lineage)

Quadrivalent vaccines will contain the same three HA antigens as trivalent vaccines, plus[4]:

- B/Phuket/3073/2013-like virus (Yamagata lineage)

There are three main types of influenza vaccines: Inactivated Influenza Vaccines (IIVs), Recombinant Influenza Vaccine (RIV4), and Live Attenuated Influenza Vaccine (LAIV4). Information regarding each of the three different types are included below and in table 1.

Inactivated Influenza Vaccines (IIVs) There are multiple IIVs available and include both trivalent and quadrivalent formulations. All standard dose, unadjuvanted IIVs will be quadrivalent, with one exception being Afluria (available as both tri and quadrivalent). Both high dose unadjuvanted IIV (HD-IIV3-Fluzone-High Dose) and adjuvanted IIV (aIIV3-Fluad) are trivalent. Adjuvanted IIVs are formulated to promote a better immune response and are designed specifically for patients ≥ 65 years of age. High dose unadjuvanted IIVs showed superior efficacy over comparator standard-dose IIV3 in a large randomized trial, and may provide better protection than standard dose IIV3 in adults ≥ 65 years of age.[5] All IIVs are contraindicated in patients who have a severe allergic reaction to the vaccine or to any components (other than egg). Two precautions for IIVs include moderate or severe acute illness with or without fever, as well as GBS (*Guillain-Barre syndrome)* within 6 weeks following a previous dose of influenza vaccine. The same contraindications and precautions hold true for the RIV4.

Recombinant Influenza Vaccine (RIV4) There is one RIV4 available for the current influenza season - Flublok Quadrivalent (RIV4). This product is indicated in patients ≥18 years of age, is manufactured without the use of the influenza viruses (no shedding of the vaccine virus occurs), and is egg -free.[5]

Live Attenuated Influenza Vaccine (LAIV4) There is one LAIV4 available for the current influenza season - FluMist Quadrivalent. This product is indicated for patients 2-49 years of age and is administered intranasally. The LAIV4 has a few more contraindications when compared to the other types of influenza vaccines. Listed below are the contraindications for LAIV4[8]:

- Patients who have a severe allergic reaction to the vaccine or to any components
- Children and adolescents receiving concomitant aspirin or salicylate containing medications
- Children aged 2-4 years of age who have received a diagnosis of asthma or whose parents or caregivers report that a healthcare provider has told them during the preceding 12 months that their child had wheezing or asthma or whose medical record indicates a wheezing episode has occurred during the preceding 12 months
- Patients who are immunocompromised due to any reason (including immunosuppression caused by medications and HIV infection)
- Close contacts and caregivers of severely immunosuppressed persons who require a protected environment
- Pregnant women
- Patients who have received influenza antiviral medication within the previous 48 hours

The LAIV4 product has the same precautions as the other products but has one additional warning for patients ≥5 years of age with asthma and presence of an underlying medical condition that might predispose to complications after wild-type influenza infection.[8]

There are three Neuraminidase Inhibitors (NAIs) currently on the market to treat influ-

enza infection, two of which are also indicated as prophylaxis during the 2018-19 influenza season. Tamiflu (oseltamivir) is an oral NAI indicated for treatment of acute, uncomplicated influenza A and B in patients ≥ 2 weeks of age who have been symptomatic for no more than 48 hours. Oseltamivir is also indicated for prophylaxis of influenza A and B in patients ≥ 1 year and older.[9] Relenza (zanamivir), an inhaled NAI, is indicated for the treatment of acute, uncomplicated influenza A and B in patients ≥ 7 years of age who have been symptomatic for no more than 48 hours. Zanamivir is also indicated for prophylaxis of influenza A and B in patients ≥ 5 year and older.[10] Rapivab (peramivir) is an I.V. NAI indicated for treatment of acute uncomplicated influenza in children ≥2 years who are not hospitalized and have been symptomatic for no more than 2 days.[11]

A fourth medication to treat influenza infection recently came to market. Xofluza (baloxavir marboxil) is a single dose oral tablet polymerase acidic (PA) endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza in patients ≥ 12 years of age who have been symptomatic for no more than 48 hours.[12]

It is important to identify patients who have contracted the influenza virus in order to start them on antiviral treatment to reduce morbidity and mortality. The best results are seen when patients are treated within 48 hours of symptom onset but, therapy can still be considered even after 48 hours of symptom onset.[7] Antiviral medications are useful in treating influenza infection, however, first line treatment against the influenza virus should always be prevention with the influenza vaccine.

Table 1. U.S. Influenza Vaccine Products for the 2018-19 Season[4]

Trade Name	Presentation	Age Indication
Quadrivalent Inactivated Influenza Vaccines (IIV4s)		
Afluria Quadrivalent	0.5 mL prefilled syringe 5.0 mL multi-dose vial	≥5 yrs ≥5 yrs (needle/syringe), 18-64 yrs (jet injector)
Fluarix Quadrivalent	0.5 mL prefilled syringe	≥6 months
FluLaval Quadrivalent	0.5 mL prefilled syringe 5.0 mL multi-dose vial	≥6 months ≥6 months
Flucelvax	0.5 mL prefilled syringe 5.0 mL multi-dose vial	≥4 yrs ≥4 yrs
Fluzone Quadrivalent	0.25 mL prefilled syringe 0.5 mL prefilled syringe 0.5 mL single dose vial 5.0 mL multi-dose vial	6 months through 35 months ≥3 yrs ≥3 yrs ≥6 months
Trivalent Inactivated Influenza Vaccines (IIV3s)		
Afluria	0.5 mL prefilled syringe 5.0 mL multi-dose vial	≥5 yrs ≥5 yrs (needle/syringe), 18-64 yrs (jet injector)
Fluad (adjuvanted)	0.5 mL prefilled syringe	≥65 yrs
Fluzone High-Dose	0.5 mL prefilled syringe	≥65 yrs
Quadrivalent Recombinant Influenza Vaccines (RIV4)		
Flublok Quadrivalent	0.5 mL prefilled syringe	≥18 yrs
Live Attenuated Influenza Vaccine (LAIV4)		
FluMist Quadrivalent	0.2 prefilled intranasal sprayer	2 through 49 yrs

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10. Relenza® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; June 2018.
11. Rapivab ® [package insert]. Durham, NC: BioCryst Pharmaceuticals, Inc.; September 2017.
12. Xofluza® [package insert]. South San Francisco, CA: Genentech USA, Inc.; October 2018.
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