Influenza Vaccines

Pink Book Web-on-Demand Series
October 18, 2022

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Learning Objectives

- Describe the Advisory Committee on Immunization Practices General Best Practice Guidelines on Immunization.
- Describe an emerging immunization issue.
- For each vaccine-preventable disease, identify those for whom routine immunization is recommended.
- For each vaccine-preventable disease, describe characteristics of the vaccine used to prevent the disease.
- Locate current immunization resources to increase knowledge of team's role in program implementation for improved team performance.
- Implement disease detection and prevention health care services (e.g., smoking cessation, weight reduction, diabetes screening, blood pressure screening, immunization services) to prevent health problems and maintain health./

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Influenza

Influenza

- **Highly infectious viral illness**
  - *Influence of the stars*
- **Virus first isolated in 1933**
  - Isolated in ferrets
- **Vaccine developed in late 1930s**

Influenza

- **Multiple pandemics throughout history**
  - First pandemic in 1580
  - At least 4 pandemics in 19th century
  - Three pandemics in the 20th century
    - Estimated 50 million deaths worldwide in pandemic of 1918-1919
    - Pandemics of 1957 and 1968 of lesser severity
  - Most recent pandemic (H1N1) in 2009-2010
- **Severity of pandemics variable**
  - But because of many infected persons, there will be a large number of severe and fatal cases

Influenza Virus

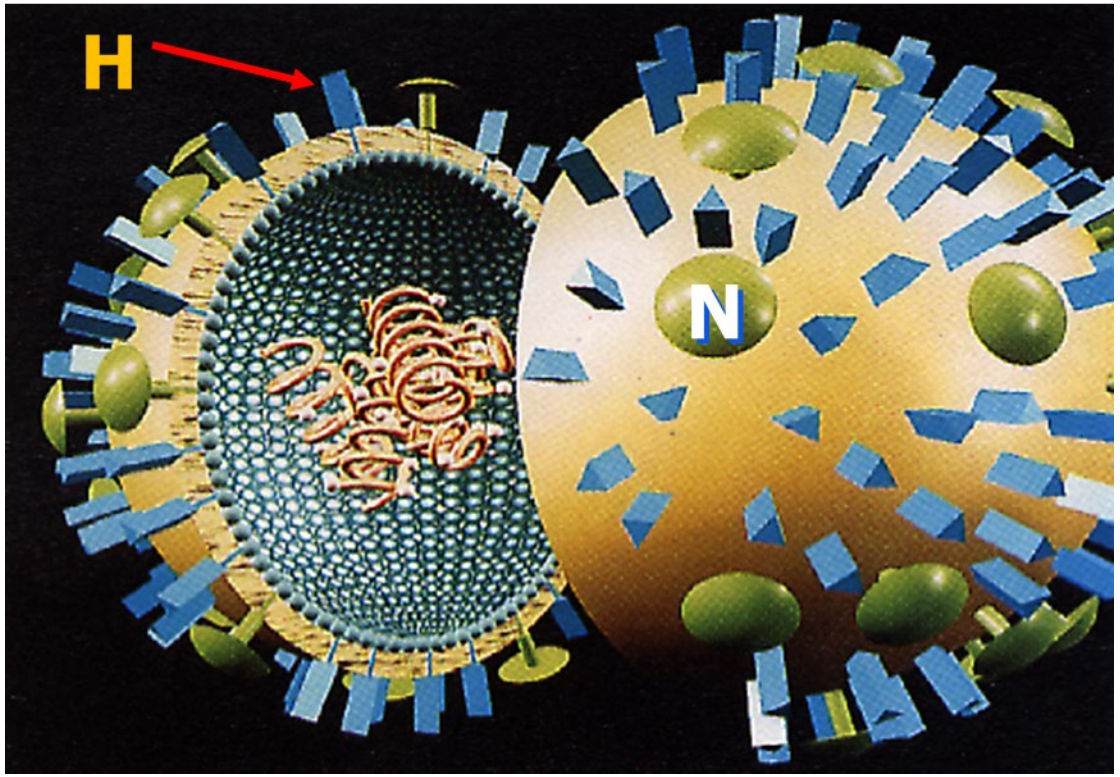
- **Single-stranded RNA virus**
- **Orthomyxoviridae family**
- **4 types: A, B, C, and D**
- **Subtypes of type A are determined by hemagglutinin and neuraminidase**
- **Influenza B viruses classified into 2 lineages**
  - Victoria
  - Yamagata

Influenza Virus Strains

- **Type A**
  - Humans and other animals
  - All age groups
  - Moderate to severe illness
- **Type B**
  - Humans only
  - Primarily affects children
  - Milder epidemics
- **Type C**
  - Rarely reported in humans
  - Most cases subclinical
  - No epidemics
- **Type D**
  - Not known to cause disease in people
  - Primarily affects cattle

Influenza Type A Subtypes

Subtypes of type A determined by hemagglutinin (H) and neuraminidase (N)



A/California/7/2009 (H1N1)

Virus type | Geographic origin | Strain number | Year of isolation | Virus subtype

Influenza Antigenic Changes

- **Antigenic drift**
  - Minor change, same subtype
  - Caused by point mutations in gene
  - May result in epidemic
  - May occur in both Influenza A and B viruses

- **Antigenic shift**
  - Major change, new subtype
  - Caused by exchange of gene segments
  - May result in pandemic
  - Occurs only with Influenza A viruses

June 12, 2009

WHO declares first flu pandemic in 41 years

Updated 6/12/2009 12:08 AM | Comments 295 | Recommend 63 E-mail | Save | Print | Reprints & Permissions | RSS

Enlarge

By Fabrice Coffrini, AFP/Getty Images

World Health Organization Director General Margaret Chan sits before Assistant Director General Keiji Fukuda at a Geneva news conference announcing that the WHO decided to raise the

By Steve Sternberg, USA TODAY

The World Health Organization scaled up its flu warning to its highest level Thursday, declaring the first global influenza pandemic in 41 years as cases of H1N1 continued to mount in the USA, Europe, Latin America and Australia.

"The scientific criteria for a pandemic have been met," said Margaret Chan, director general of the WHO. "The world is now at the start of the 2009 influenza pandemic."

PHOTOS: Schools closed in Hong Kong, Vermont (and more)
INTERACTIVES: World map, how H1N1 strain emerged
FAQ: What you should know about swine flu
VIDEO: Reporters answer your questions

The decision marks the agency's formal recognition of the magnitude of the challenge posed by a novel, H1N1 flu virus now spreading unchecked among people who, because the virus is new, are virtually all susceptible to it.

The WHO is working closely with vaccine makers, who are just wrapping up production of seasonal flu vaccine for fall and gearing up to produce the first doses of an H1N1 vaccine by September. The agency urged member nations to maintain their vigilance to detect ominous changes in the virus's

Influenza Pathogenesis

- **Respiratory transmission of virus**
- **Replication in respiratory epithelium with subsequent destruction of cells**
  - Regeneration of the epithelium takes 3-4 weeks
- **Viremia rarely documented**
- **Virus shed in respiratory secretions for 5–10 days**

Influenza Clinical Features

- **Can range from asymptomatic to severe infection**
- **Incubation period 2 days (range 1–4 days)**
- **50% of infected persons develop classic symptoms**
  - Onset of symptoms is sudden
- **Abrupt onset of fever 38°C through 39°C (usually 101˚through 102˚F), myalgia, sore throat, nonproductive cough, headache**
  - Illness usually lasts between 3-7 days

Influenza Complications

- **Pneumonia**
  - Secondary bacterial pneumonia
  - Primary influenza pneumonia
- **Exacerbations of underlying respiratory conditions**
- **Encephalitis, aseptic meningitis, transverse myelitis, myocarditis, pericarditis, Guillain-Barré syndrome**
- **Reye Syndrome**
- **Death reported in fewer than one per 1,000 cases**

Groups at Increased Risk for Influenza Complications and Severe Illness

- Children age 6–59 months and adults age 65 years and older (children under 6 months of age are also at high risk, but cannot be vaccinated)
- Persons with chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)
- Immunosuppressed persons
- Persons who are or will be pregnant during the influenza season
- Children and adolescents (age 6 months to 18 years) who are receiving aspirin therapy and who might be at risk for experiencing Reye syndrome after influenza virus infection
- Residents of nursing homes and other long-term care facilities
- American Indians/Alaska Natives
- Persons who are extremely obese (BMI greater than or equal to 40 for adults)

Influenza Epidemiology

Influenza Epidemiology	
Reservoir	Human, animals
Transmission	Respiratory, droplets/aerosol, direct contact
Temporal pattern	Peak December–March in temperate climate May occur earlier or later
Communicability	1 day before to 5-7 days after onset (adults) or 10 days after onset (children)

Influenza Diagnosis

- **Clinical and epidemiological characteristics**

- **Diagnostic tests include:**
  - Molecular assays
  - Antigen detection tests

- **Tests used for surveillance or research:**
  - Isolation of influenza virus from clinical specimens (e.g., throat, nasopharynx, sputum)
  - Significant rise in influenza IgG by serologic assay

Influenza Surveillance

- Monitor prevalence of circulating strains and detect new strains
- Estimate influenza-related morbidity, mortality, and economic loss
- Rapidly detect outbreaks
- Assist disease control through rapid preventive action

Immunogenicity, Efficacy, and Effectiveness of Seasonal Influenza Vaccines

- **Duration of immunity less than one year due to waning and antigenic drift**
- **Estimates of vaccine efficacy and effectiveness depend on many factors**
  - Study design, diagnostic testing measures, and the outcome being measured
  - Age and immunocompetence of the vaccine recipient
  - Degree of similarity of the vaccine strain(s) to the circulating strain(s)
  - Type of vaccine administered

https://www.cdc.gov/flu/vaccines-work/effectivenessqa.htm; Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Hall E., Wodi A.P., Hamborsky J., et al., eds. 14th ed. Washington, D.C. Public Health Foundation, 2021. https://www.cdc.gov/vaccines/pubs/pinkbook/flu.html#Vaccines

Immunogenicity, Efficacy, and Effectiveness of Seasonal Influenza Vaccines (Continued)

- **Vaccination is effective in reducing the risk of influenza illness by 40% to 60% in the overall population when vaccine strains and circulating viruses are similar**
  - Circulating A/H3N2 influenza viruses drifted significantly after strain selection for the 2014–2015 vaccines, contributing to a lower vaccine efficacy of 19% during that season
- **In general, current flu vaccines tend to work better against influenza B and influenza A(H1N1) viruses and offer lower protection against influenza A(H3N2) viruses**

https://www.cdc.gov/vaccines/pubs/pinkbook/flu.html; https://www.cdc.gov/flu/vaccines-work/vaccineeffect.htm

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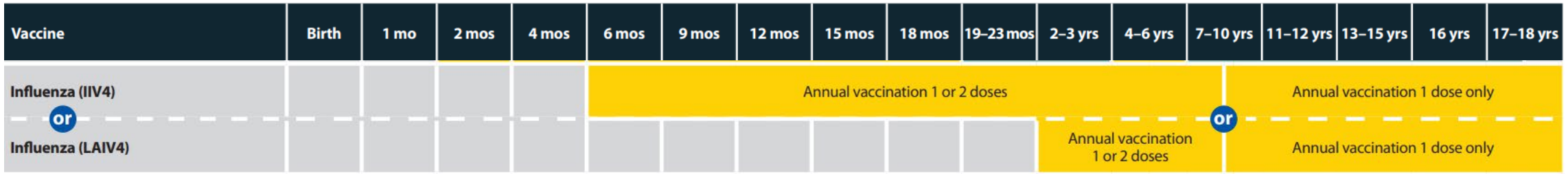
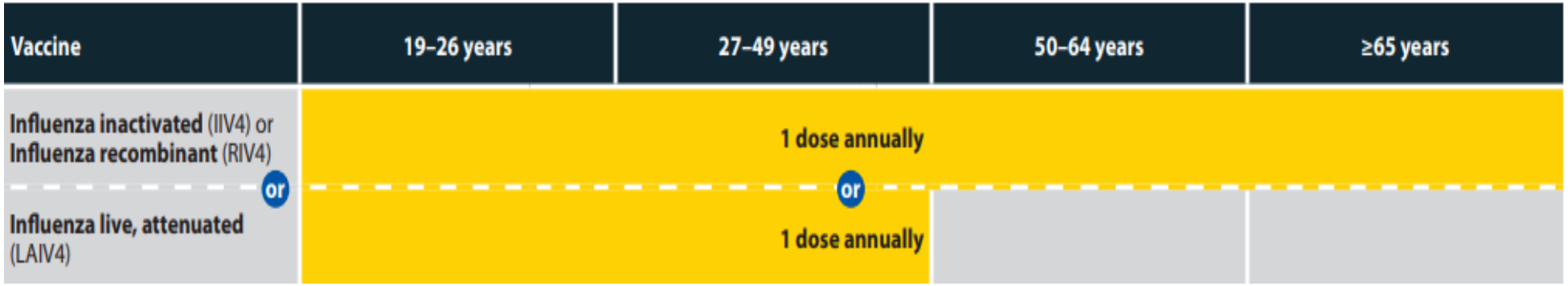
Influenza Vaccines

Influenza: Child and Adult Vaccination Schedule





- Non-live and live vaccines
- Administered by Intramuscular injection (IM) (non-live vaccines) or intranasal administration (live vaccine)

2022–2023 Influenza Vaccine Strains: HA

- **Egg-based/live vaccine**
  - A/Victoria/2570/2019 (H1N1)pdm09-like virus
  - A/Darwin/9/2021 (H3N2)-like virus
  - B/Austria/1359417/2021 (Victoria lineage)-like virus
  - B/Phuket/3073/2013 (Yamagata lineage)-like virus
- **Cell-culture/recombinant**
  - A/Wisconsin/588/2019 (H1N1)pdm09-like virus
  - A/Darwin/6/2021 (H3N2)-like virus
  - B/Austria/1359417/2021 (Victoria lineage)-like virus
  - B/Phuket/3073/2013 (Yamagata lineage)-like virus

Abbreviations

- **IIV = Inactivated influenza vaccine**
- **RIV= Recombinant influenza vaccine**
- **LAIV = Live, attenuated influenza vaccine**
- **Prefixes (apply to IIVs):**
  - SD = standard dose
  - HD = high dose
  - a = adjuvanted
  - cc = cell-culture-based
- **Numeric suffixes (e.g., RIV3, IIV4) indicate trivalent or quadrivalent, respectively**
  - All currently-available vaccines are quadrivalent

Influenza Vaccines

- **IIV**
  - Contain inactivated virus, split or subunit
    - Standard dose or high dose
    - Unadjuvanted or adjuvanted
    - Egg- or cell-culture-based
    - Many brands, some approved for those as young as 6 months of age
    - Intramuscular (IM) administration
- **RIV**
  - Contain recombinant HA
  - Egg-free
  - IM administration
- **LAIV**
  - Live, attenuated virus
  - Attenuated (to not cause clinical illness) and cold-adapted
  - Intranasal (NAS) administration

https://www.cdc.gov/mmwr/volumes/67/wr/mm6722a5.htm?s_cid=mm6722a5_w and https://www.cdc.gov/mmwr/volumes/67/rr/pdfs/rr6703a1-H.pdf

Available Influenza Vaccines

Trade name *Manufacturer*	Available presentations	Approved age indications	Volume per dose by age group
Quadrivalent IIVs (IIV4s)—Standard-dose—Egg-based (15 µg HA per virus component in 0.5 mL; 7.5 µg HA per virus component in 0.25 mL)			
Afluria Quadrivalent *Seqirus*	0.5 mL prefilled syringe 5.0 mL multidose vial*	≥3 yrs† ≥6 mos (needle/syringe)† 18 through 64 yrs (jet injector)	≥3 yrs—0.5 mL† 6 through 35 mos—0.25 mL†
Fluarix Quadrivalent *GlaxoSmithKline*	0.5 mL prefilled syringe	≥6 mos	≥6 mos—0.5 mL
FluLaval Quadrivalent *GlaxoSmithKline*	0.5 mL prefilled syringe	≥6 mos	≥6 mos—0.5 mL
Fluzone Quadrivalent *Sanofi Pasteur*	0.5 mL prefilled syringe 0.5 mL single-dose vial 5.0 mL multidose vial*	≥6 mos§ ≥6 mos§ ≥6 mos§	≥3 yrs—0.5 mL§ 6 through 35 mos—0.25 mL ***or*** 0.5 mL§
Quadrivalent IIV (ccIIV4)—Standard-dose—Cell culture-based (15 µg HA per virus component in 0.5 mL)			
Flucelvax Quadrivalent *Seqirus*	0.5 mL prefilled syringe 5.0 mL multidose vial*	≥6 mos ≥6 mos	≥6 mos —0.5 mL
Quadrivalent IIV (HD-IIV4)—High-dose—Egg-based (60 µg HA per virus component in 0.7 mL)			
Fluzone High-Dose Quadrivalent *Sanofi Pasteur*	0.7 mL prefilled syringe	≥65 yrs	≥65 yrs—0.7 mL
Adjuvanted quadrivalent IIV4 (aIIV4)—Standard-dose with MF59 adjuvant—Egg-based (15 µg HA per virus component in 0.5 mL)			
Fluad Quadrivalent *Seqirus*	0.5 mL prefilled syringe	≥65 yrs	≥65 yrs—0.5 mL
Quadrivalent RIV (RIV4)—Recombinant HA (45 µg HA per virus component in 0.5 mL)			
Flublok Quadrivalent *Sanofi Pasteur*	0.5 mL prefilled syringe	≥18 yrs	≥18 yrs—0.5 mL
Quadrivalent LAIV (LAIV4)—Egg-based (contains $10^{6.5\text{-}7.5}$ fluorescent focus units/0.2 mL)			
FluMist Quadrivalent *AstraZeneca*	0.2 mL prefilled single-use intranasal sprayer	2 through 49 yrs	0.1 mL each nostril (0.2 mL total)

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Quick Aside about Influenza Vaccines for Children 6 Months–35 Months of Age

- **All unadjuvanted, standard-dose IIV4s are now approved for ages ≥6 months**
  - Five licensed products, but the dose volume differs for some for ages 6 through 35 months
    - Afluria Quadrivalent: 0.25 mL (0.25 mL prefilled syringes not available)
    - Fluarix Quadrivalent: 0.5 mL
    - FluLaval Quadrivalent: 0.5 mL
    - Fluzone Quadrivalent: 0.25 mL or 0.5 mL (0.25 mL prefilled syringes not available)
    - Flucelvax Quadrivalent 0.5 mL
- **Dose volume is distinct from number of doses needed**
  - A child 6 months through 35 months who should receive 2 doses of influenza vaccine still needs the second dose of vaccine 4 weeks later, even if they received a 0.5 mL initial dose

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Clinical Considerations

Groups Recommended for Vaccination

- **Routine annual influenza vaccination is recommended for all persons 6 months of age or older who do not have contraindications**

- **While vaccination is recommended for everyone in this age group, there are some for whom it is particularly important:**
  - People age 6 months and older who are at high risk of complications and severe illness
  - Contacts and caregivers of these people and of infants younger than 6 months (because there is no vaccine approved for children this age)

Adults Age 65 years and Older

- **Adults aged ≥65 years should preferentially receive any one of the following influenza vaccines**
  - HD-IIV4
  - RIV4
  - aIIV4
- **If none of these three vaccines is available at an opportunity for vaccine administration, then any other age appropriate influenza vaccine should be used**

Timing of Vaccination

- **Vaccination should occur before onset of influenza activity.**
- **For most persons who need only one dose of influenza vaccine, vaccination should ideally be offered during:**
  - September
  - October
- **Vaccination should continue throughout the season as long as virus is circulating**
- **Vaccination in July and August not recommended for most groups**
  - Children 6 months through 8 years who require 2 doses should receive the first dose as soon as vaccine is available

Influenza Vaccination of Pregnant People

- **Influenza vaccination recommended by ACIP since 2004 for people who are or will be pregnant during influenza season**
  - Increased risk for severe influenza illness in pregnant people, particularly during second and third trimesters
- **Pregnant people may receive any licensed, recommended, age-appropriate IIV or RIV, during any trimester**
- **LAIV is contraindicated during pregnancy**
  - But can be used post-partum

Influenza Vaccination of Persons with COVID-19

- Persons in isolation for COVID-19 or in quarantine for known or suspected exposures should not be vaccinated if vaccination will pose an exposure risk to others in the vaccination setting
- For persons who are moderately or severely ill, vaccination should be deferred until they have recovered
- For persons who are mildly ill or asymptomatic, deferral might be considered to avoid confusing COVID-19 illness symptoms with postvaccination reactions

CoAdministration of Influenza and COVID-19 Vaccines

- **Providers should offer influenza and COVID-19 vaccines at the same visit if the recipient is due for both vaccines**
  - High-dose or adjuvanted influenza vaccines should be administered in separate limbs

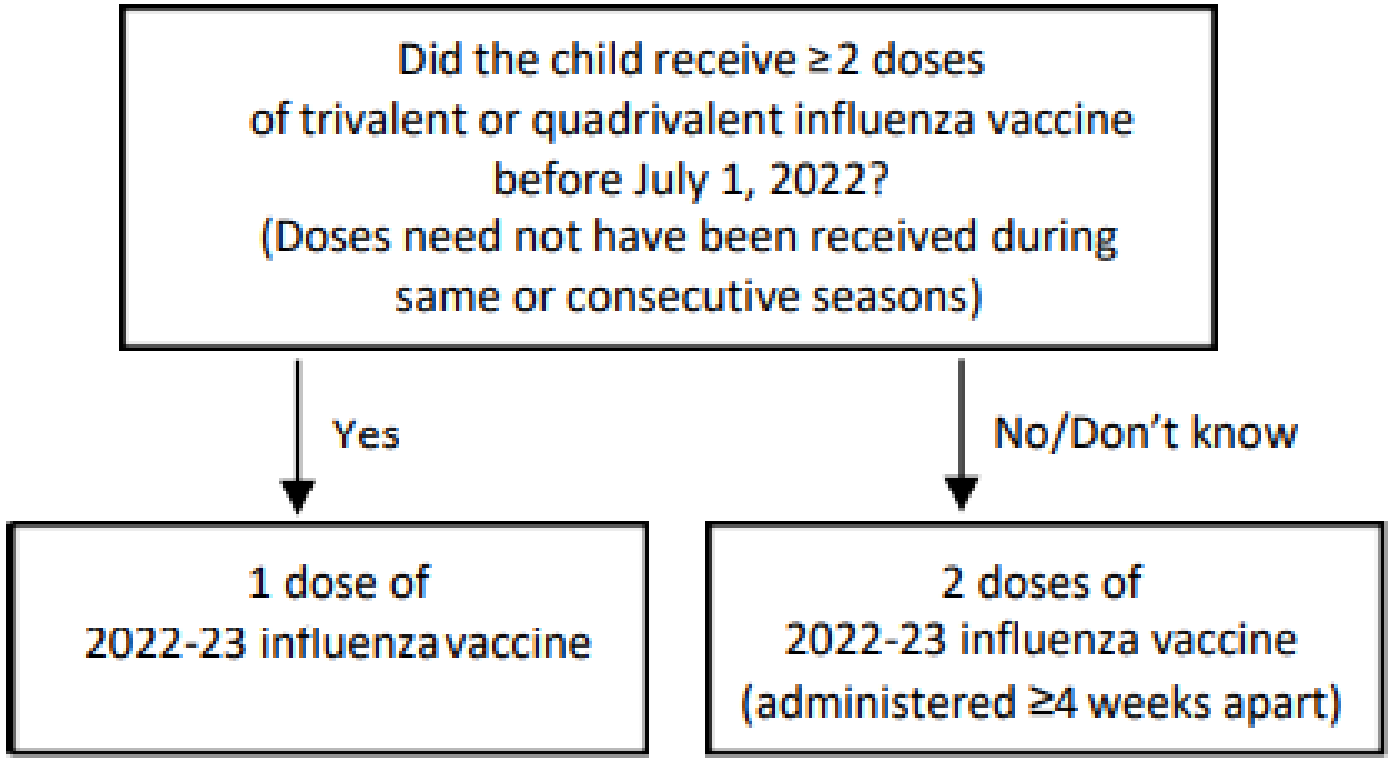
CoAdministration of Influenza and Other Vaccines

- **IIV and RIV may be administered concurrently or sequentially with other live or inactivated vaccines**
  - Injectable vaccines given simultaneously should be administered at separate anatomic sites
- **LAIV4 may be administered simultaneously with other inactivated or live vaccines**
  - If not given simultaneously, then ≥4 weeks should pass between administration of LAIV4 and another live vaccine

Influenza Vaccination of Persons with Egg Allergy

- **Persons who have experienced only hives after exposure to egg may receive any licensed, recommended vaccine that is otherwise appropriate**
- **Persons with a history of severe allergic reaction to egg (e.g., angioedema, respiratory distress, lightheadedness, recurrent emesis, required epinephrine or other emergency intervention) may also receive any licensed, recommended vaccine that is otherwise appropriate**
  - If a vaccine other than ccIIV4 or RIV4 is selected, it should be administered in an inpatient or outpatient medical setting, supervised by a health care provider who can recognize and manage severe allergic reactions.

Dosing Algorithim for Children Age 6 Months through 8 Years



- If 2 cumulative doses received prior to July 1, 2022, only 1 dose needed for 2022-2023
- Only 1 dose needed after the 9th birthday
- For children aged 8 years who require 2 doses of vaccine, both doses should be administered even if the child turns age 9 years between receipt of dose 1 and dose 2

Knowledge Check

- **You are administering influenza vaccine to a 71-year old patient with no contraindications or precautions to vaccination. Which of the following vaccine should NOT be used:**

- **A. HD-IIV**
- **B. aIIV**
- **C. LAIV**
- **D. RIV**

Answer

- **You are administering influenza vaccine to a 71-year old patient with no contraindications or precautions to vaccination. Which of the following vaccine should NOT be used:**

- ~~A. HD-IIV~~
- ~~B. aIIV~~
- **C. LAIV**
- ~~D. RIV~~

Knowledge Check

- A child just turned 9 years old yesterday. One month ago, he received his first ever dose of influenza vaccine. Should he receive another dose of influenza vaccine this season?

- A. Yes
- B. No

Answer

- **A child just turned 9 years old yesterday. One month ago, he received his first ever dose of influenza vaccine. Should he receive another dose of influenza vaccine this season?**
  - **A. YES**

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Safety

Contraindications

Egg-based IIV	ccIIV	RIV
History of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine (other than egg), or to a previous dose of any influenza vaccine (any egg-based IIV, ccIIV, RIV, or LAIV of any valency)	History of severe allergic reaction (e.g., anaphylaxis) to ccIIV of any valency, or to any component of ccIIV4	History of severe allergic reaction (e.g., anaphylaxis) to RIV of any valency, or to any component of RIV4

Contraindications

LAIV
History of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine (other than egg) or to a previous dose of any influenza vaccine (i.e, any egg-based IIV, ccIIV, RIV, or LAIV of any valency)
Concomitant aspirin or salicylate-containing therapy in children and adolescents
Children aged 2 through 4 years who have received a diagnosis of asthma or whose parents or caregivers report that a health care 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
Children and adults who are immunocompromised due to any cause, including but not limited to medications, congenital or acquired immunodeficiency states, HIV infection, anatomic asplenia, or functional asplenia (e.g., due to sickle-cell anemia)
Close contacts and caregivers of severely immunosuppressed persons who require a protected environment
Pregnancy
Persons with active communication between the CSF and the oropharynx, nasopharynx, nose, or ear or any other cranial CSF leak
Persons with cochlear implants (due to potential for CSF leak, which might exist for some period of time after implantation. Providers might consider consultation with a specialist concerning risk of persistent CSF leak if an age-appropriate inactivated or recombinant vaccine cannot be used)
Receipt of influenza antiviral medication within the previous 48 hours for oseltamivir and zanamivir, 5 days for peramivir, and 17 days for baloxavir

Precautions

Egg-based IIV	ccIIV	RIV
Moderate or severe acute illness with or without fever	Moderate or severe acute illness with or without fever	Moderate or severe acute illness with or without fever
History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine	History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine	History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine
	History of severe allergic reaction to a previous dose of any other influenza vaccine (any egg-based IIV, RIV, or LAIV of any valency)	History of severe allergic reaction to a previous dose of any other influenza vaccine (any egg-based IIV, ccIIV, or LAIV of any valency)

Precautions

LAIV
Moderate or severe acute illness with or without fever
History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine
Asthma in persons aged ≥5 years
Other underlying medical conditions that might predispose to complications from influenza (e.g., chronic pulmonary, cardiovascular [except isolated hypertension], renal, hepatic, neurologic, hematologic, or metabolic disorders [including diabetes mellitus])

Adverse Reactions

Inactivated Influenza Vaccine (IIV)*
Local reactions (soreness, redness)
Fever, malaise, myalgia
Allergic reactions (hives, angioedema, anaphylaxis)
Guillain-Barré syndrome

*Common local and systemic reactions for RIV are similar to those for IIVs

Adverse Reactions

Live Attenuated Influenza Vaccine (LAIV)	
Children	**Adults**
Increased risk of wheezing in children 6–23 months of age	Significantly increased rate of cough, runny nose, nasal congestion, sore throat, and chills reported among vaccine recipients

Knowledge Check

- **Which of the following is a contraindication to LAIV?**
- **A. Pregnancy**
- **B. Immunosuppression**
- **C. History of severe allergic reaction to a component of the vaccine**
- **D. Concomitant aspirin therapy in a child or adolescent**
- **E. All of the above.**

Answer

- **Which of the following is a contraindication to LAIV?**

- ~~A. Pregnancy~~
- ~~B. Immunosuppression~~
- ~~C. History of severe allergic reaction to a component of the vaccine~~
- ~~D. Concomitant aspirin therapy in a child or adolescent~~
- **E. All of the above.**

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Storage and Handling

Influenza Vaccine Storage and Handling

- **Always consult manufacturer package inserts**
- **Typically store between 2°C and 8°C (36°F and 46°F)**
  - Never expose vaccine to freezing temperatures
- **Protect from light**
- **Vaccines should not be used beyond the expiration date on the label.**
  - In addition to the expiration date, multidose vials also might have a beyond-use date (BUD), which specifies the number of days the vaccine can be kept once first accessed
  - After being accessed for the first dose, multidose vials should not be used after the BUD. If no BUD is provided, then the listed expiration date is to be used.

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Resources

Influenza Resources

- **ACIP's influenza recommendations web page**
  - https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html

- **Immunization Action Coalition influenza web page**
  - https://www.immunize.org/influenza/

- **Children's Hospital of Philadelphia Vaccine Education Center influenza web page**
  - http://www.chop.edu/centers-programs/vaccine-education-center/vaccine-details/influenza-vaccine#.VgHMa3YpCAU

Continuing Education Information

- **CE credit, go to**: https://tceols.cdc.gov/
- **Search course number: WD4564-101822**
- **CE credit expires: July 1, 2024**
- **CE instructions are available on the Pink Book Web-on-Demand Series web page**
- **Questions and additional help with the online CE system, e-mail** CE@cdc.gov

E-mail Your Immunization Questions to Us

- NIPINFO@cdc.gov

Thank You From Atlanta!