What's New with the Flu?

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Disclosures

No disclosures

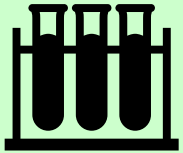
Current funding from NHLBI, CDC, PCORI, AHRQ

Objectives

Summarize the current epidemiology of influenza in children



Evaluate the performance characteristics of point of care testing



Describe the current guidelines for treatment



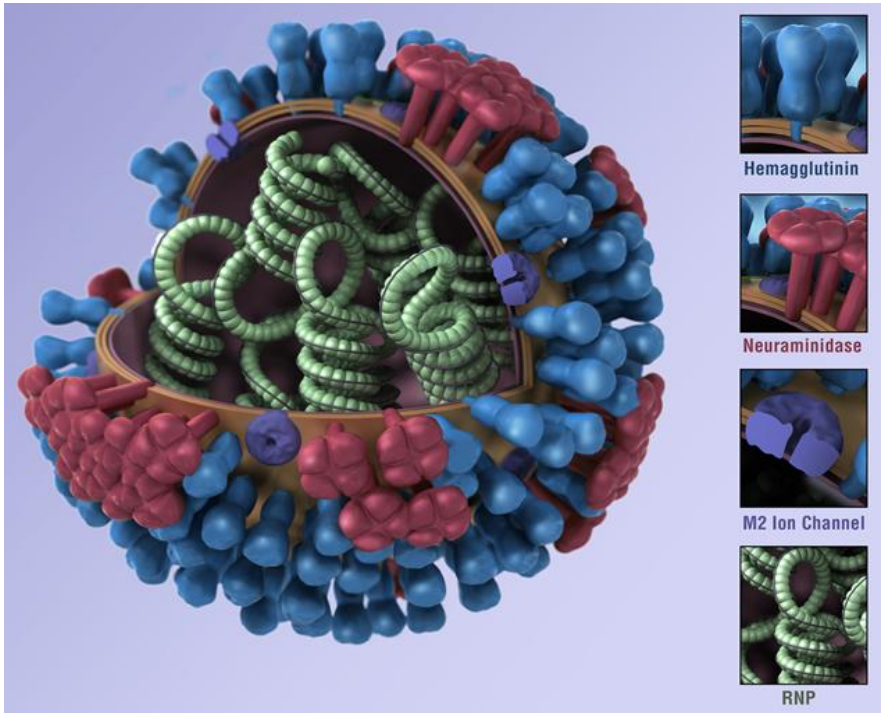
Synthesize knowledge about vaccines to make a strong recommendation





Virology 101

Parts of influenza virus



- Segmented RNA- enables gene re-assortment
- Antigenic shift- responsible for pandemics
- HA- 19 types, contribute to pandemics, determines severity, antibodies confer protection
- Antigenic drift- why we need to change flu vaccine each year and get annual vaccine
- NA- 11 types, target for antiviral drugs

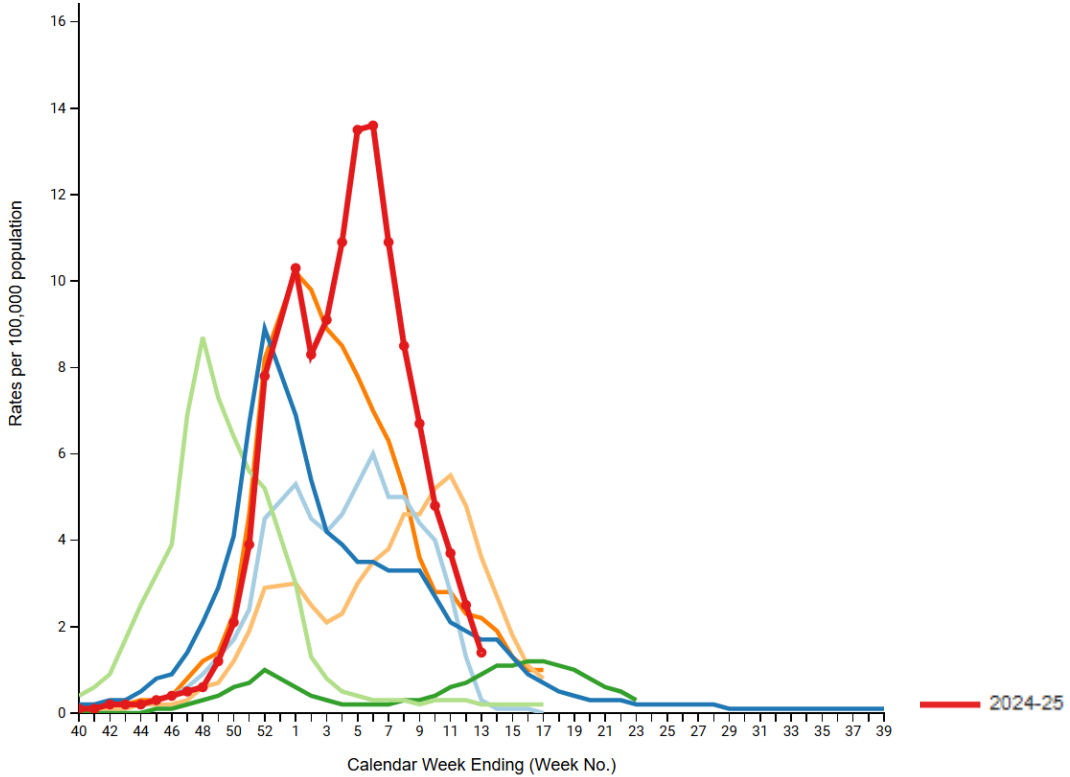
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The most severe influenza season since 2009 H1N1 pandemic

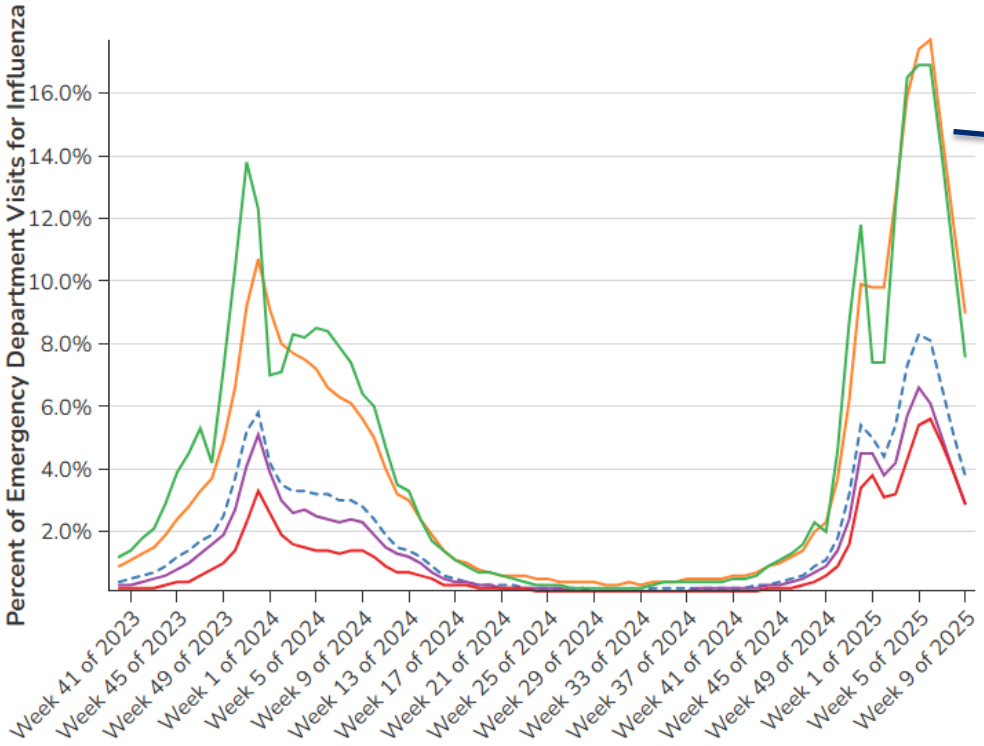


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https://www.cdc.gov/flu/weekly/index.htm

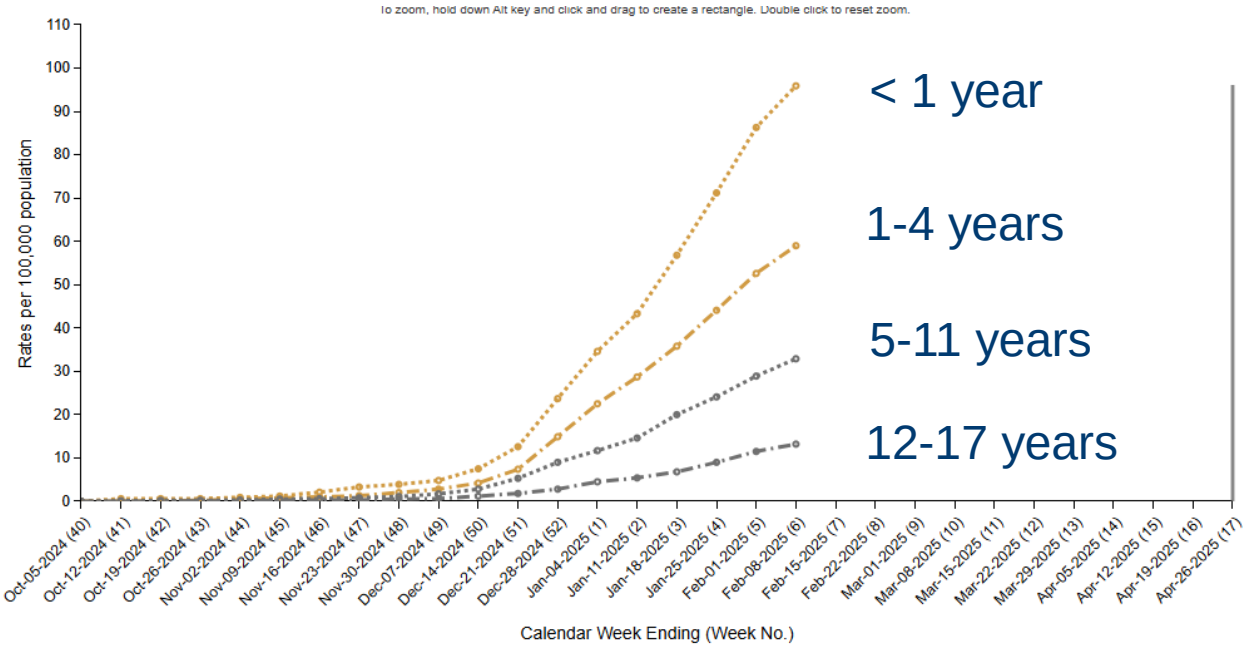
Highest percentage of ED visits for influenza are in children



0-4 year olds
5-17 year olds

https://www.cdc.gov/flu/weekly/index.htm

Pediatric hospitalization rates by age in the US, 2024-25



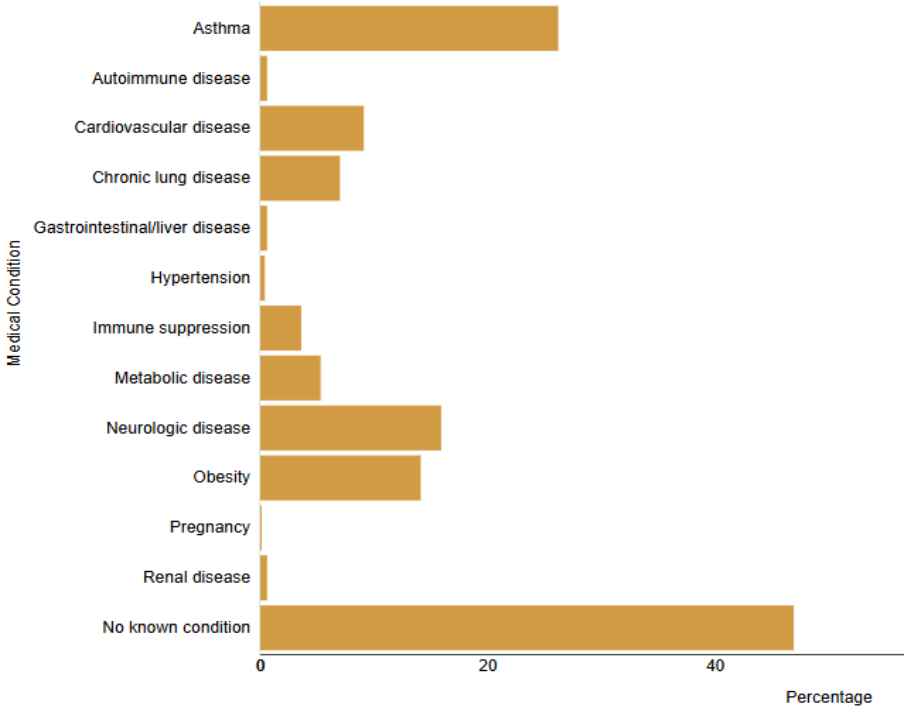
Highest rates of hospitalizations are in those < 1 year of age

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https://www.cdc.gov/flu/weekly/index.htm

Underlying medical conditions among those hospitalized



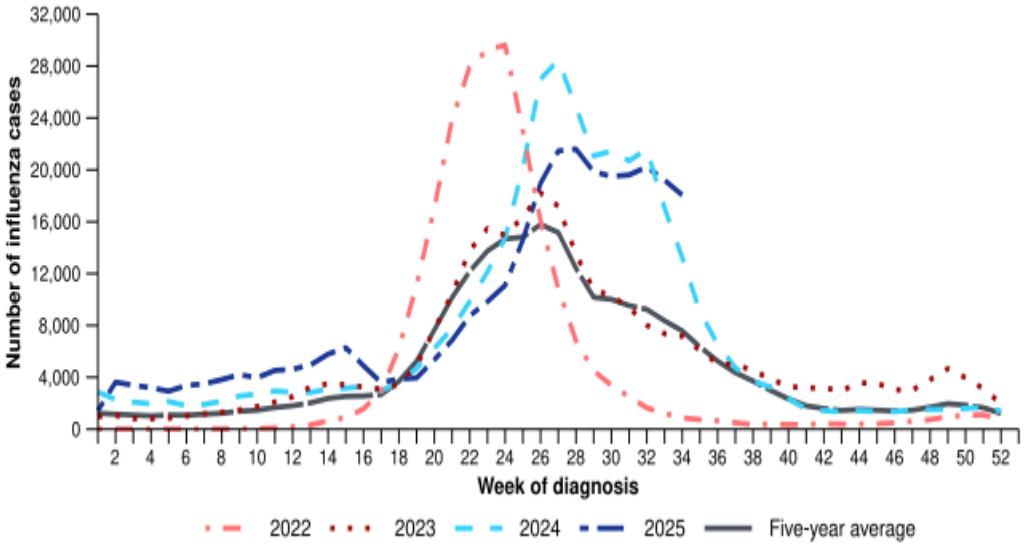
Most children admitted - no underlying medical condition
Of those with underlying medical conditions- asthma, neurologic disease, obesity
Higher proportion of males (56%)
17% end up in the ICU
21% diagnosed with pneumonia
66% received an antiviral

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https://www.cdc.gov/flu/weekly/index.htm

Influenza in Australia, 2025 season



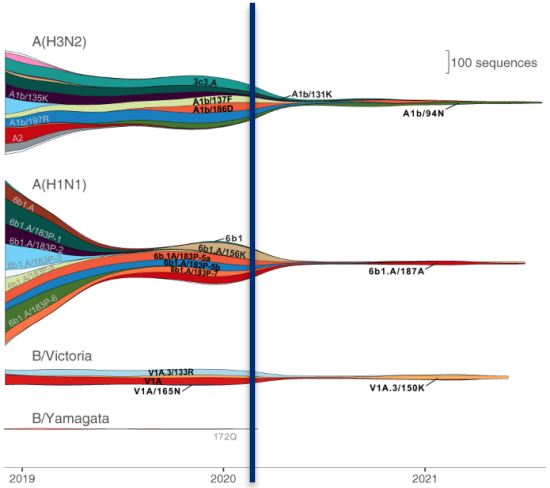
- Worst year on record for influenza adjusted for population
- 25.7% 6 months – 5 years were vaccinated in 2025, lowest since 2021
- > 65yr rates 60.5% rate - lowest since 2020

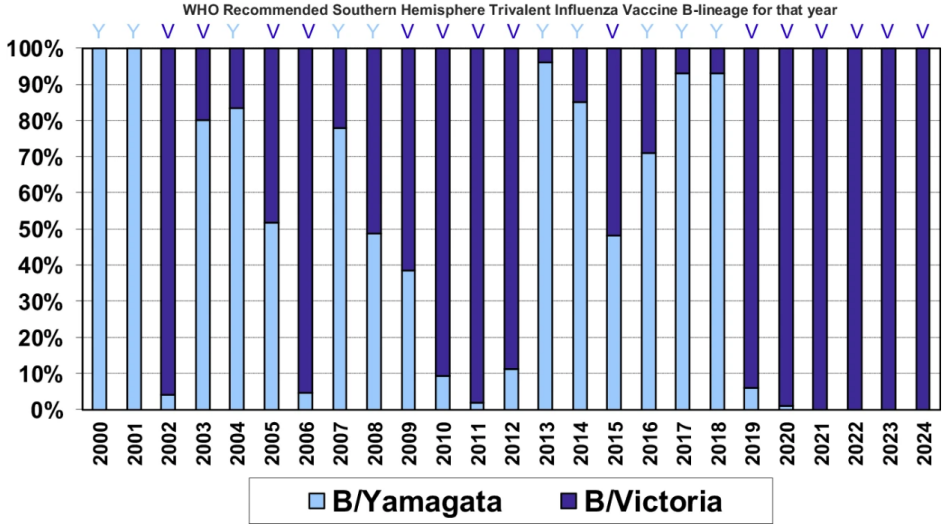
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Influenza lineage circulation, 2000-2024

Influenza B/Yamagata lineage has not been seen since April 2020





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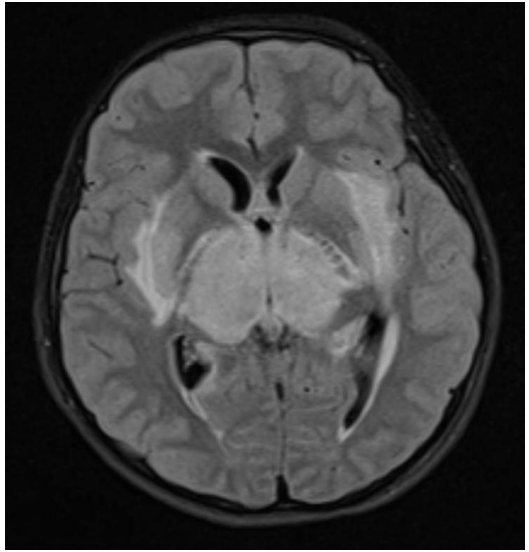
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Dhanasekaran V et al. Nature Communications 13, 1721 (2022)
Barr et al. NPJ Vaccines 219 (2024)


Clinical Updates

Acute Necrotizing Encephalitis

- Multiple and symmetric brain lesions and involvement of systemic organs leading to DIC or multi-organ failure in the severest cases
- Thalamus bilaterally, internal capsule, basal ganglia, cerebellum and brainstem tegmentum (areas located around ventricular system)
- Excessive production and action of proinflammatory cytokines
- A/w RANBP2 mutations



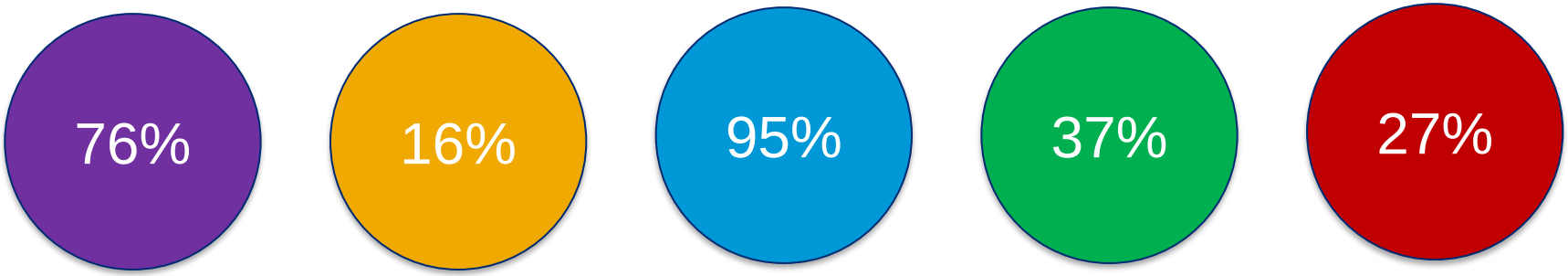
Acute necrotizing encephalitis. Coronal FLAIR magnetic resonance image of a 7-year-old patient with influenza-associated encephalitis demonstrating bilateral confluent signal hyperintensity in the white matter and thalami.

M Mizuguchi et al. J. Neurol Neurosurg Psychiatry. 1995 May; 58(5): 555-61

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National Case series in US Acute Necrotizing Encephalitis, n = 41, 23 US hospitals



No prior medical history

Received influenza vaccine

Influenza A

RANBP2 mutation (tested for in 30 pts)

Mortality


H5N1 Update

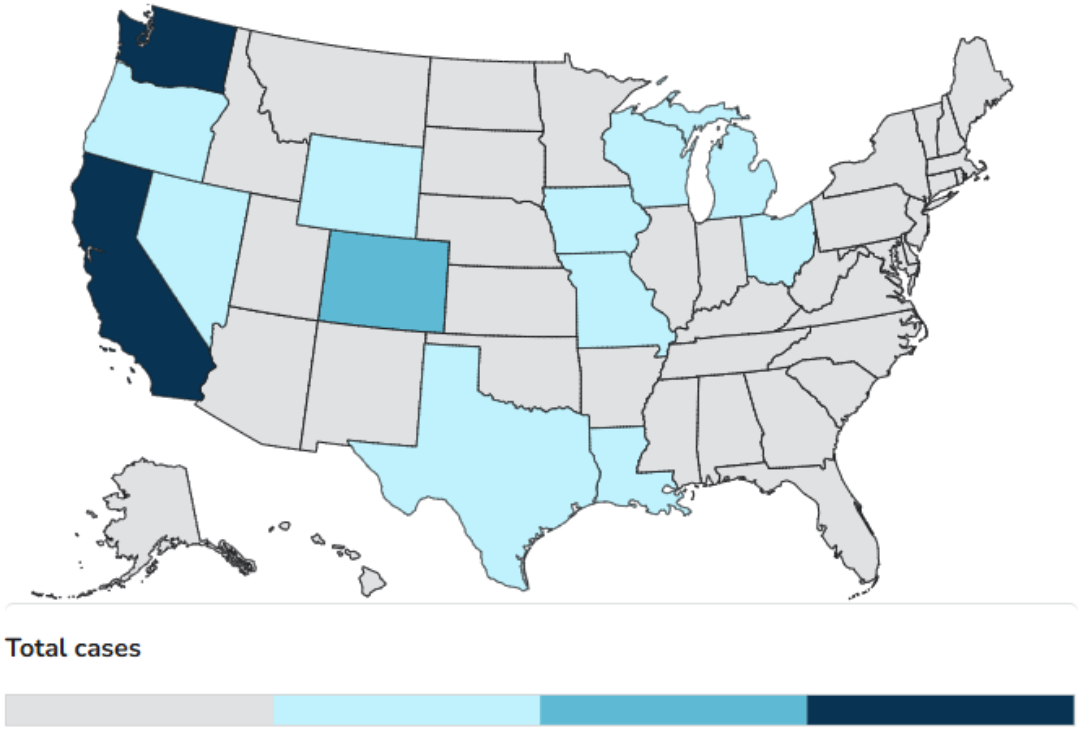
Human cases of H5N1 in the US

National Total Cases: 70

Cases	Exposure Source
41	Dairy Herds (Cattle)*
24	Poultry Farms and Culling Operations*
2	Other Animal Exposure†
3	Exposure Source Unknown‡

NOTE: One additional case was previously detected in a poultry worker in Colorado in 2022. Louisiana reported the first H5 bird flu death in the U.S.

*Exposure Associated with Commercial Agriculture and Related Operations
†Exposure was related to other animals such as backyard flocks, wild birds, or other mammals
‡Exposure source was not able to be identified



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https://www.cdc.gov/bird-flu/situation-summary/index.html

H5N1- what the pediatric community should know

17 States with outbreaks in cattle, 50 states with outbreaks in poultry	Identified in pasteurized milk but not viable virus	Seasonal vaccination does not produce antibody protection
Susceptible to oseltamivir- preferred treatment at this time	Clinical illness ranges from mild to severe/critical disease	Closely related to two existing HPAI A(H5N1) candidate vaccine viruses

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Avoid consuming unpasteurized milk and products

Cook poultry, eggs, and beef to a safe internal temperature

Avoid exposures to sick or dead wild birds, poultry, domesticated birds, and other wild or domesticated animals (including cows)

Test if respiratory symptoms/conjunctivitis with exposure– (panel tests not subtypeable, sent to health department for testing

Influenza and SARS-CoV-2 testing

Testing methods

Method	Detection	Acceptable specimens	Test time	CLIA waived
RIDT 	Antigen detection	NP or nasal swab/ aspirate/wash, throat swab	< 15 min	Yes
DIA 	Antigen detection	NP or nasal swab/ aspirate/wash, throat swab	15-30 min	Yes
NAAT 	Nucleic acid detection	NP or nasal swab	1-4 hrs	Yes
RT-PCR 	Nucleic acid detection	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	Varies by assay 1-8 hrs	No

Ref: CDC https://www.cdc.gov/flu/professionals/diagnosis/overview-testing-methods.htm

At home testing















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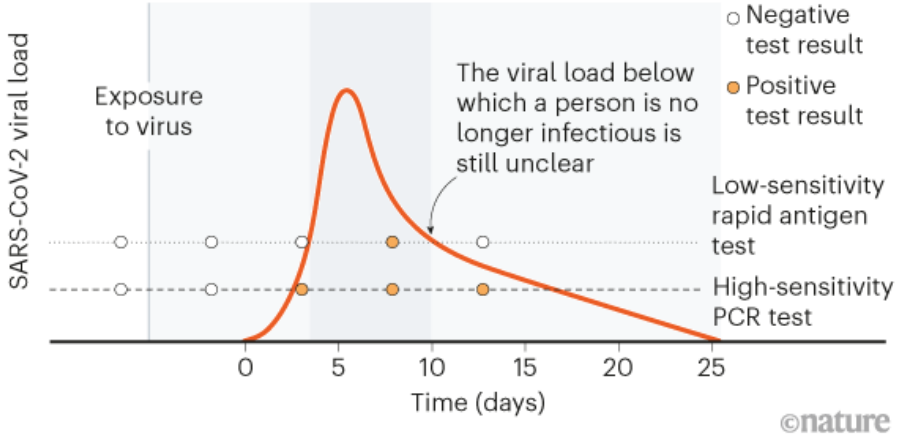
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Source: Amazon.com

Molecular testing vs antigen testing

Test positive by PCR 1-2 days before antigen test

Similar sensitivity when VL high, but more variable when VL is low



Antigen tests now need to have sensitivity of at least 80%

Serial testing 24-36 hrs apart preferred with rapid tests

More likely to be contagious if positive antigen test

Antigen tests more reliable during season, can trust positive test

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Treatment

Influenza Treatment



oseltamivir



zanamivir



peramivir

Neuraminidase inhibitors



baloxavir

Endonuclease inhibitor

Influenza Treatment



oseltamivir

Preferred agent for influenza at this time

Oseltamivir can be given down to the newborn period

SE in 10-15% of courses: nausea, vomiting



zanamivir

Breath activated inhaler device

7 years of age and older

Not recommended in patients with underlying airway disease due to risk of bronchospasm.



peramivir

Not superior to oseltamivir, so given if unable to provide enteral oseltamivir

Diarrhea, behavioral changes, neutropenia



baloxavir

Children 5 years of age and older

Well-tolerated

Avoid administration with dairy, calcium fortified drinks or polyvalent cations

National Guidelines – AAP, CDC, IDSA

Hospitalized with influenza

Outpatients with severe or progressive illness

Outpatients who are high risk of complications

Children < 2 years, pregnant women and those within 2 weeks postpartum (IDSA)

Consider: Outpatients within 2 days of illness onset

Consider: Children with high-risk household contacts, esp. immunocompromised

Source: CDC, AAP, IDSA guidelines

High Risk Conditions

- < 5 years (especially < 2)
- (≥ 65 years)
- Chronic pulmonary including asthma
- Neurologic and neurodevelopmental conditions
- Immunosuppression
- Cardiovascular
- Metabolic disorders including diabetes mellitus, obesity
- Renal, hepatic, hematologic
- Pregnancy and 2 weeks post-partum
- Native Americans/Alaska Natives
- Long term aspirin therapy

https://www.cdc.gov/flu/highrisk/index.htm

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

Recent meta-analysis influenza antivirals

JAMA Internal Medicine | Original Investigation

Antiviral Medications for Treatment of Nonsevere Influenza
A Systematic Review and Network Meta-Analysis

Ya Gao, PhD; Yunli Zhao, MD; Ming Liu, PhD; Shuyue Luo, MD; Yamin Chen, PhD; Xiaoyan Chen, MD; Qingyong Zheng, MD; Jianguo Xu, MD; Yanjiao Shen, MD; Wanyu Zhao, MD; Zhifan Li, MD; Sha Huang, MD; Jie Huang, MD; Jinhui Tian, PhD; Gordon Guyatt, MD; Qiukui Hao, MD

- 73 trials with 34,332 participants
- RCTs that compared direct-acting influenza antiviral drugs to no intervention, placebo, standard care, or another antiviral drug
- Outcomes including mortality, admission to hospital, admission to intensive care unit (ICU), serious adverse events

Gao et al. JAMA Int Med 2025

Results and measurements for Oseltamivir	Certainty of evidence	Summary	
Relative risk: 0.84 (95% CI 0.34-2.07), n =12,008, 17 studies	High	Oseltamivir has little or no effect on **mortality** for low-risk patients	
Relative risk: 0.84 (95% CI 0.34-2.07), n =12,008, 17 studies	High	Oseltamivir has little or no effect on **mortality** for high-risk patients	
Relative risk: 0.8 (95% CI 0.54-1.18), n =12,589, 20 studies	High	Oseltamivir has little or no effect on **admission to hospital** for low-risk patients	
Relative risk: 0.8 (95% CI 0.54-1.18), n =12,589, 20 studies	High	Oseltamivir has little or no effect on **admission to hospital** for high-risk patients	
Relative risk: 1.23 (95% CI 1.10-1.39), n =6,782, 12 studies	Moderate	Oseltamivir likely increases **adverse events** related to treatments	
Risk difference: 0.0 (95% CI -0.003-0.0002), n = 14,718, 22 studies	Moderate	Oseltamivir likely has little to no effect on **serious adverse events**	
Mean difference 0.75 lower (0.93 lower-0.57 lower), n = 9078, 22 studies	Moderate	Oseltamivir likely has no important effect on time to **alleviation of symptoms**	

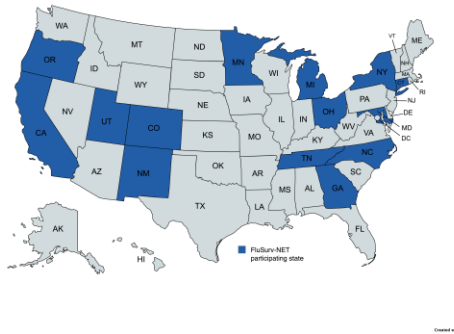
Gao et al. JAMA Int Med 2025

Results and measurements for Baloxavir	Certainty of evidence	Summary	
Relative risk: 0.83 (95% CI 0.14-4.82), n =2,144, 2 studies	High	Baloxavir has little or no effect on **mortality** for low-risk patients	
Relative risk: 0.83 (95% CI 0.14-4.82), n =2,144, 2 studies	High	Baloxavir has little or no effect on **mortality** for high-risk patients	
Relative risk: 0.24 (95% CI 0.05-1.1), n =1,461, 2 studies	High	Baloxavir has little or no effect on **admission to hospital** for low-risk patients	
Relative risk: 0.24 (95% CI 0.05-1.1), n =1,461, 2 studies	Low	Baloxavir may reduce the risk of **admission to hospital** for high-risk patients	
Relative risk: 0.74 (95% CI 0.57-0.95), n =2,776, 3 studies	High	Baloxavir does not increase **adverse events** related to treatments	
Risk difference: 0.001 (95% CI -0.004-0.005), n = 2,776, 3 studies	Moderate	Baloxavir likely has little to no effect on **serious adverse events**	
Mean difference 1.02 lower (1.41 lower-0.63 lower), n = 1,855, 3 studies	Moderate	Baloxavir likely reduces time to **alleviation of symptoms**	

Gao et al. JAMA Int Med 2025

Effectiveness of antivirals for hospitalized children





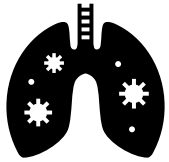
- Retrospective cohort study using FluSurv-NET data
- <18 years of age 14/15 – 22/23 seasons, n = 7103
- Adjusted Cox proportional hazard models evaluating effectiveness of oseltamivir in reducing ICU and LOS, adjusting for important covariates
- ICU admission: aHR 0.69 (95% CI 0.60,0.80) aHR <1.00 means decreased hazard of ICU admission
- Hospital LOS: aHR 1.13 (95% CI 1.06-1.21) aHR >1.00 means higher hazard of discharge, or shorter LOS

Influenza vaccination

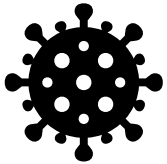
Sterilizing immunity versus disease mitigation



Natural and vaccine-induced memory can prevent severe disease



Short incubation period and can replicate before elimination by immune system



Undergoes mutations so immunity to re-exposures not as precise



Vaccine unable to generate potent mucosal immunity



Waning antibody levels over time

Current influenza vaccine recommendations ACIP

Routine annual influenza vaccination of all persons aged ≥6 months who do not have contraindications

Offer vaccines in any healthcare setting

All influenza vaccines marketed in the US are trivalent (no Yamagata), no product preference

Ideally vaccinate before the end of October, but can also continue during the influenza season

New ACIP committee update 2025

- Recommended that influenza vaccines are free of thimerosal even though there is no evidence of harm from the preservative (multi-dose vials)

- Vaccines with thimerosal are still approved by the FDA

Vaccine type		0-6 months	6-23 months	2-17 years	18-49 years	50-64 years	≥ 65 years
IIV3	Standard-dose, unadjuvanted Inactivated IIV3		Afluria trivalent Fluarix trivalent FluLaval trivalent Fluzone trivalent				
	Cell-culture based inactivated (ccIIV3)		Flucelvax trivalent				
	Adjuvanted inactivated (aIIV3)						Fluad trivalent
	High-dose inactivated (HDIIV3)						Fluzone high-dose trivalent
RIV3	Recombinant (RIV3)				Flublox trivalent		
LAIV3	Live attenuated (LAIV4)			FluMist trivalent			

Indicated for pediatric population

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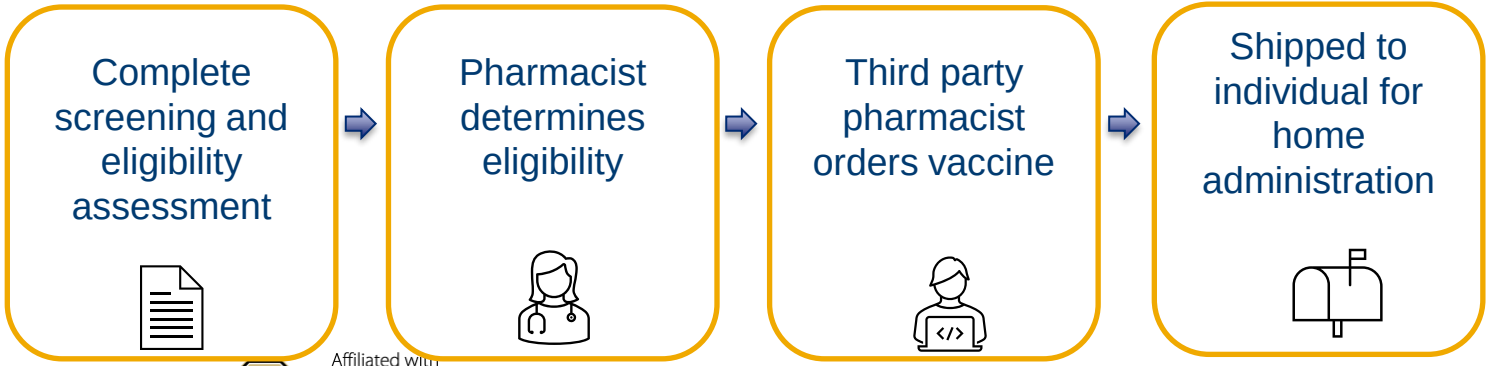
Adapted from ACIP meeting June 24, 2021

Live attenuated influenza vaccine - at home administration 2025-26 season

Ages 2-49 years

Available through third-party online pharmacy FluMist Home

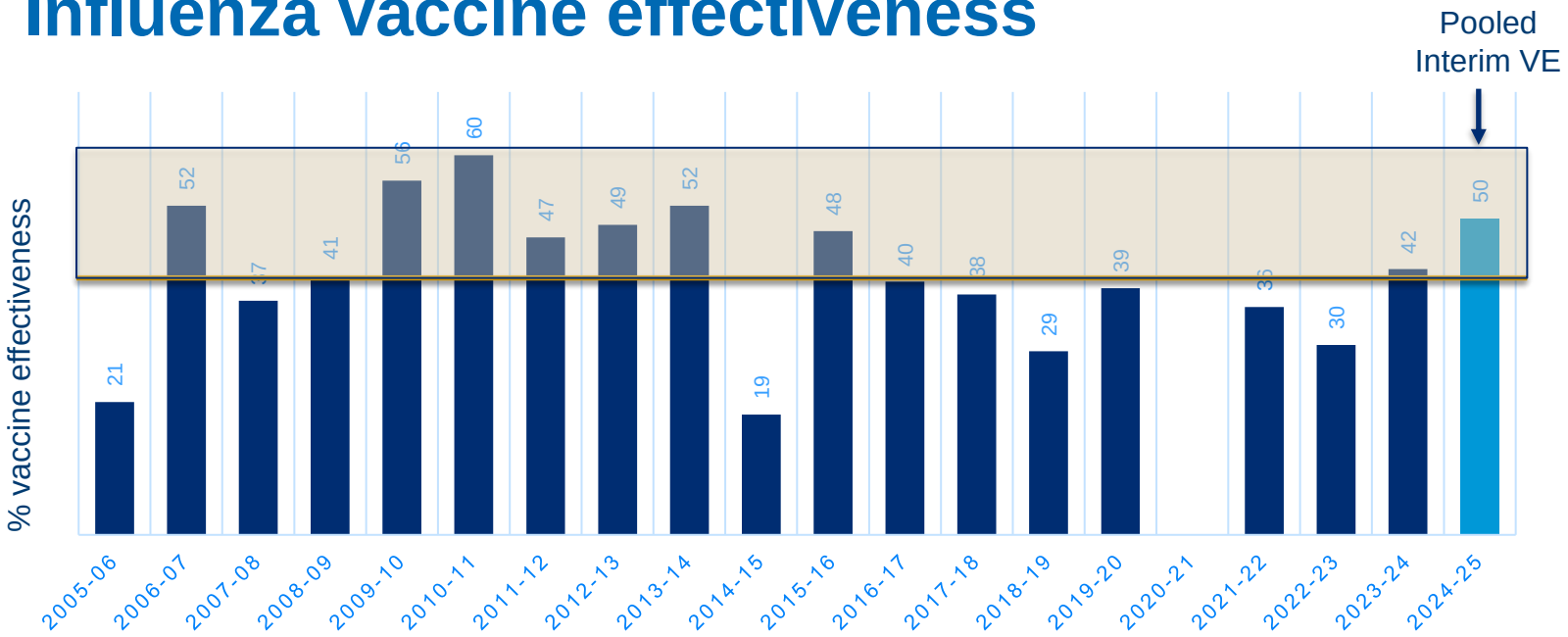
Supporting ordering, delivering, and documentation of self/caregiver administration



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Influenza vaccine effectiveness



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Interim Estimates of 2024–25 influenza VE

4 influenza vaccine effectiveness networks (IVY, NVSN, US Flu VE, VISION)

	Outpatient visits	Hospitalization
6 months to 17 years, all influenza	59 (47-68) 32 (1-54) 60 (56 - 63)	 63 (41-76) 78 (60-89)
6 months to 17 years, influenza A H1N1	72 (59-81) 53 (3-79)	63 (30-81)
6 months to 17 years, influenza A H3N2	42 (19-58) 16 (–34-49)	55 (14–77)
> 18 years, all influenza	36 (16 to 51) 56 (52 to 56)	41 (28-52) 55 (51 to 59)
> 18 years, influenza A H1N1	42 (8 to 64)	39 (−14-67)
> 18 years, influenza A H3N2	25 (–6 to 48)	51 (22-69)

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Frutos AM et al. MMWR Morb Mortal Wkly Rep 2025;74:83–90

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Vaccine effectiveness higher in:

- Children compared with adults
- Hospitalization compared with outpatient visits
- H1N1 compared with H3N2 infections

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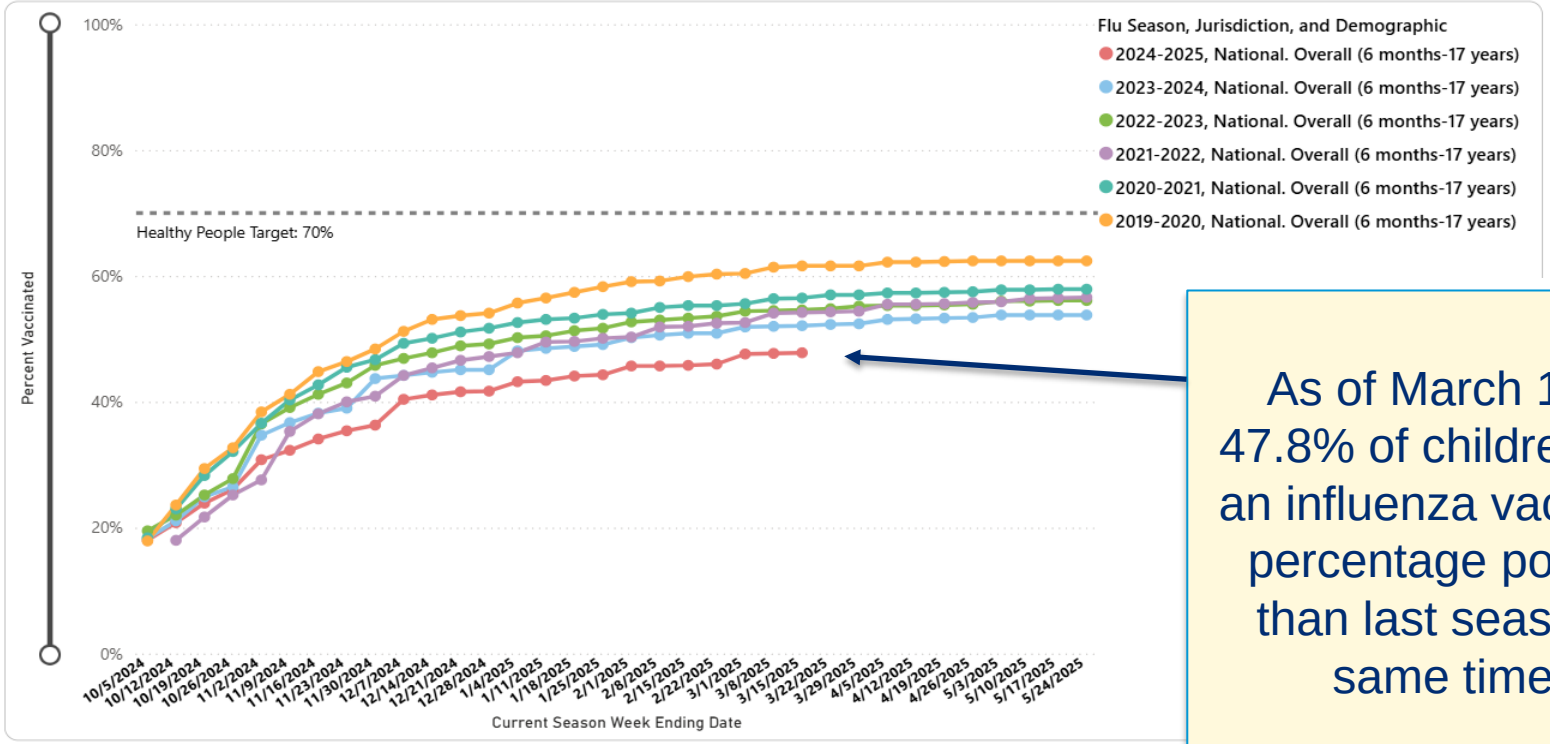
Vaccines prevented an estimated 240,000 hospitalizations, mostly in adults > 65 years

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Frutos AM et al. MMWR Morb Mortal Wkly Rep 2025;74:83–90

Decrease in vaccine uptake for influenza vaccines since COVID pandemic



As of March 15, 2025, 47.8% of children received an influenza vaccination, 5 percentage points lower than last season at this same time point

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https://www.cdc.gov/fluvaxview/dashboard/children-vaccination-coverage.html

How to make a strong influenza vaccine recommendation

- Normalize the process - *We routinely provide influenza vaccination to our patients at CHCO and have reserved a vaccine for your child.*
- Use presumptive language - *We can take care of your child's flu vaccine during this visit/hospital stay.*
- Be respectful of their concerns- *Do you mind if I ask why you are not wanting your child to receive the flu vaccine today?*
- Tailor the discussion to address concerns - *Thanks for letting me know about your concerns. I've been thinking a lot about this and we get a lot of education about influenza vaccines- would it be alright if I shared some of this information with you?*
- Find common ground - *I know you are a wonderful parent, and you want to do what's best for your child. We also want to do everything possible to keep your child as healthy as possible, and vaccination is one of those ways.*

Influenza virus-based

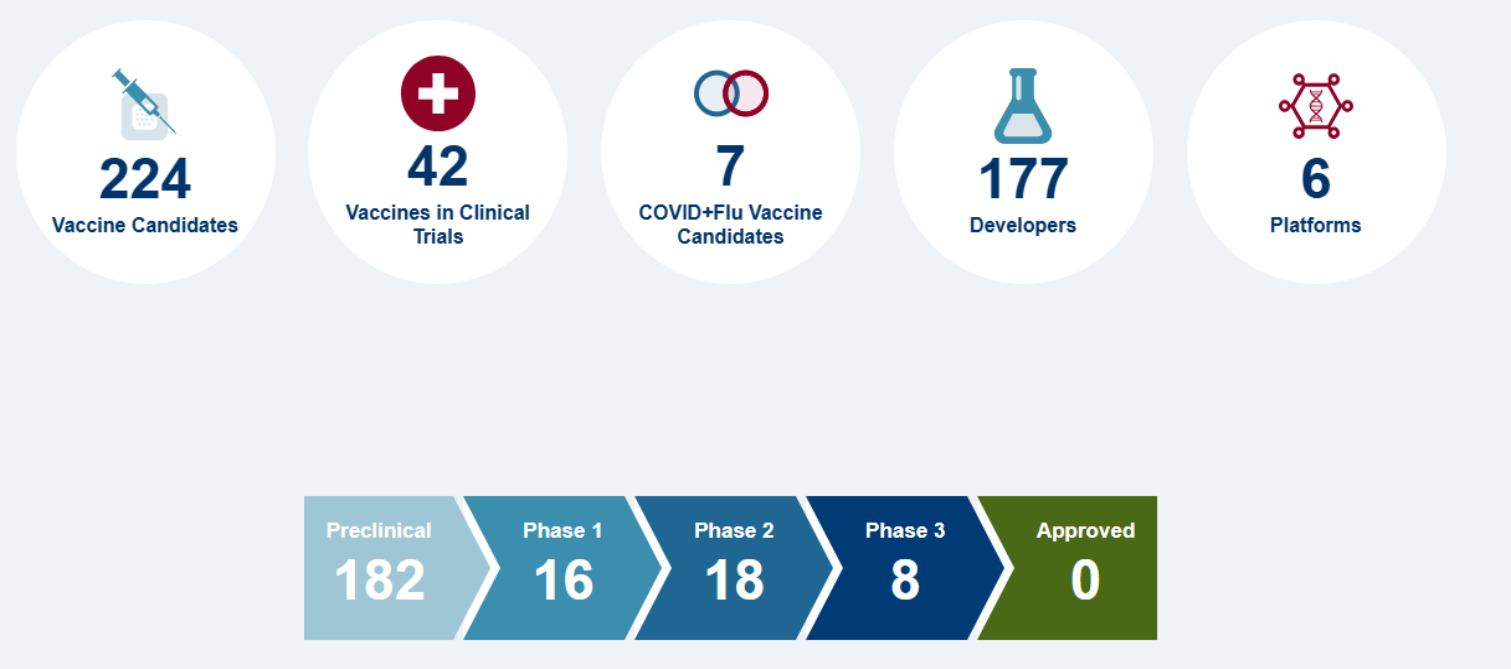
Nucleic acid-based

Non-VLP nanoparticles

Virus-vectored

Recombinant proteins

VLP nanoparticles

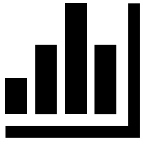


Children's Hospital Colorado
Here, it's different.

Affiliated with
School of Medicine
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Main takeaway points



2024-25 most severe influenza season in 15 years



H5N1 transmission in mammals, signals increased transmission risk to humans, no human-human transmission currently



Combined RIDT plus NAAT are now available for at home testing, improved performance characteristics



Treatment – national guidelines recommend for hospitalized and those at high risk



Focus messaging on preventing severe disease, vaccine uptake declining

Questions?