What's New With the Flu?

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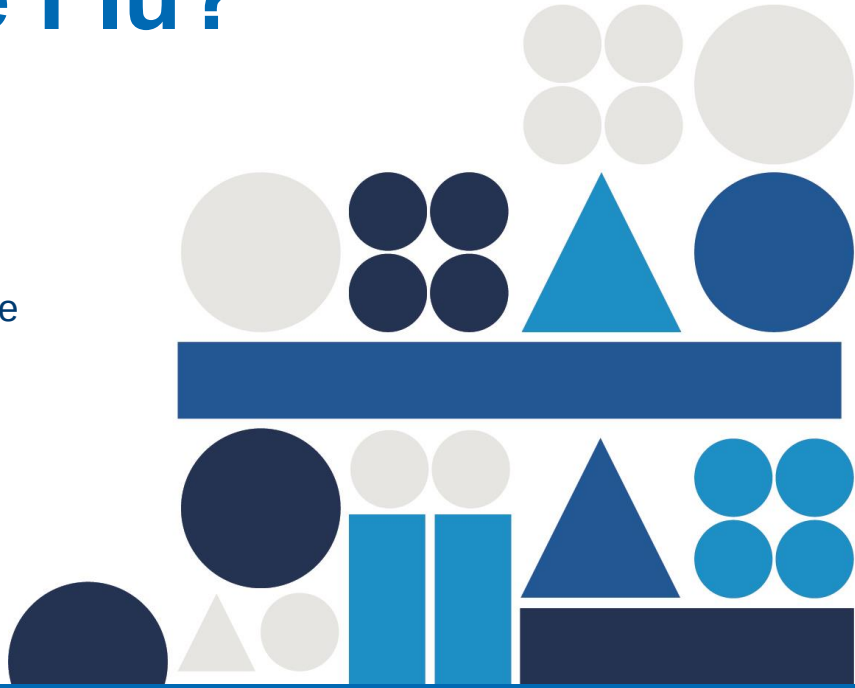

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Disclosures

No current disclosures

Objectives

Discuss the current epidemiology of influenza

Review the current situation for H5N1 including pandemic potential

Summarize influenza testing and treatment recommendations

Understand rationale for updates on influenza vaccination recommendations

Topics we will cover

Epidemiology 

Treatment 

Testing 

Vaccination 

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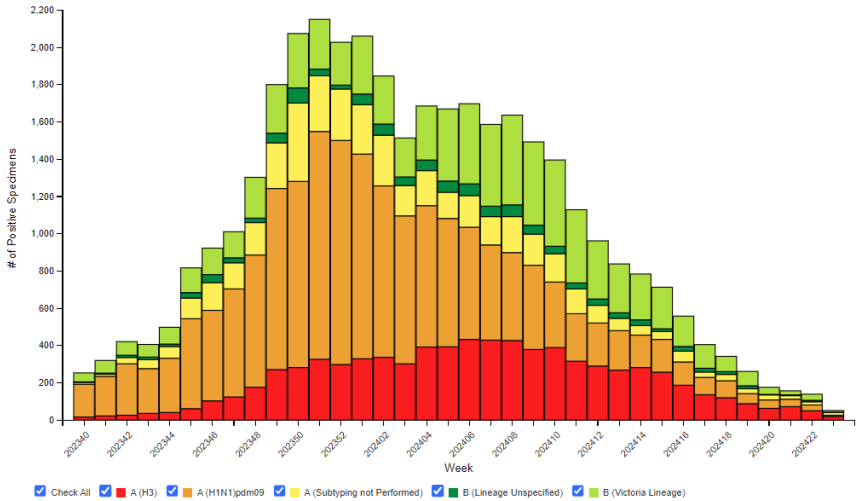
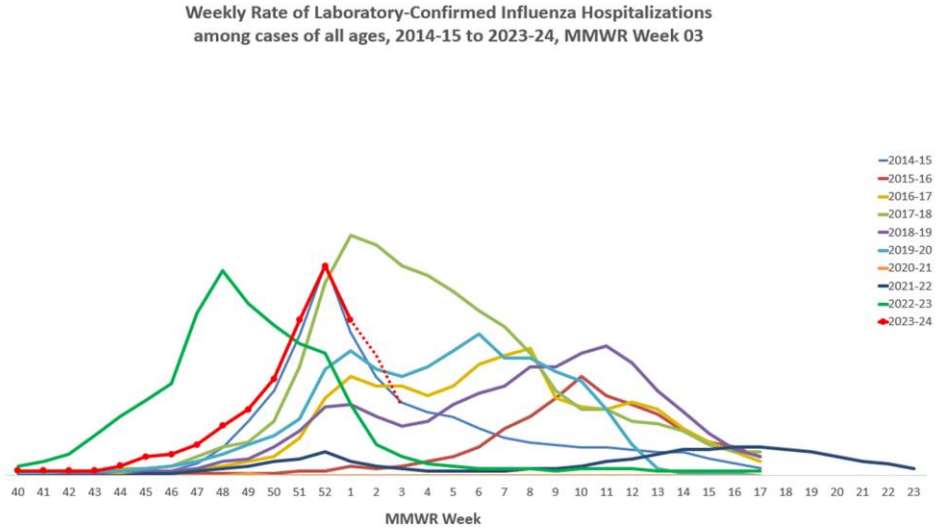
Influenza has returned to pre-pandemic levels

Influenza A and B co-circulating
Mostly influenza A H1N1





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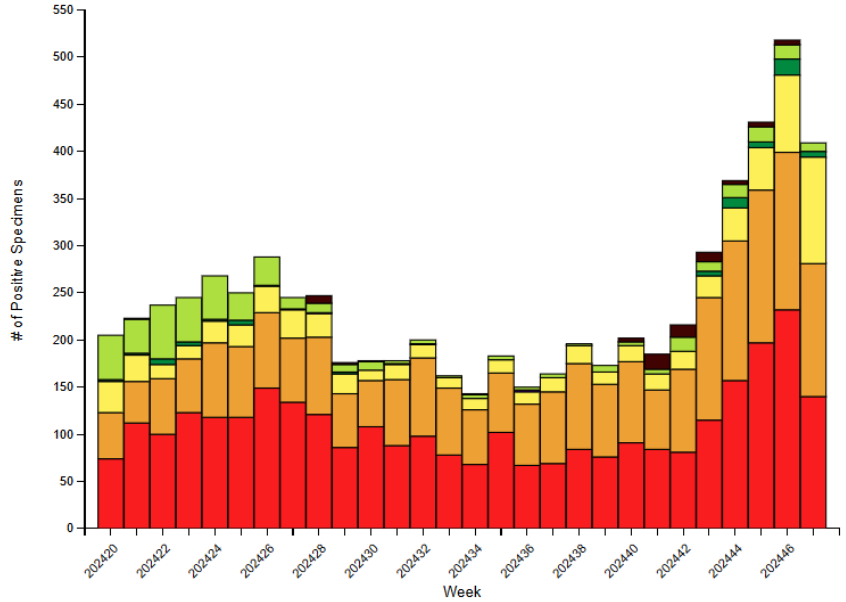
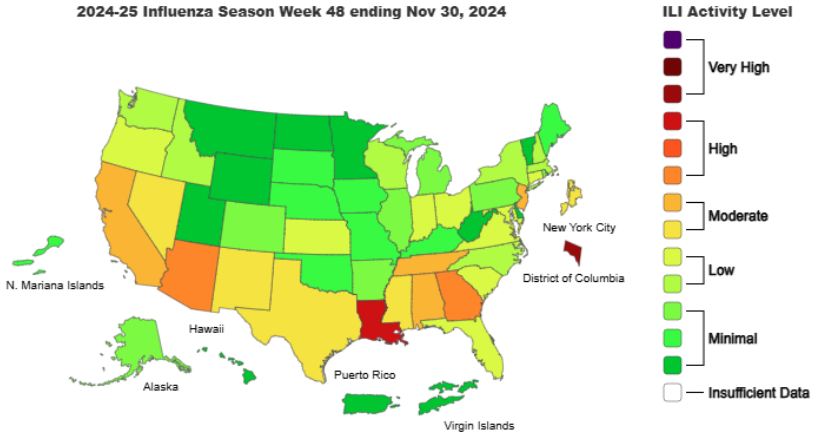
https://www.cdc.gov/flu/weekly/index.htm

Influenza Activity in the US, 2024

Influenza A H1N1 and H3N2 currently circulating
little influenza B activity





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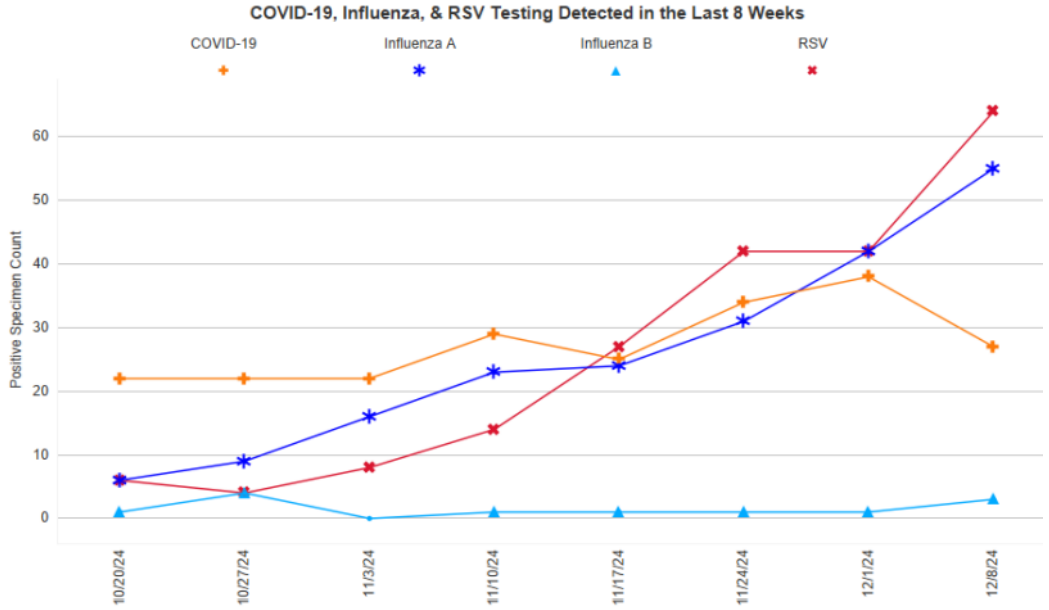
Children's Hospital Colorado Data

Bug Watch



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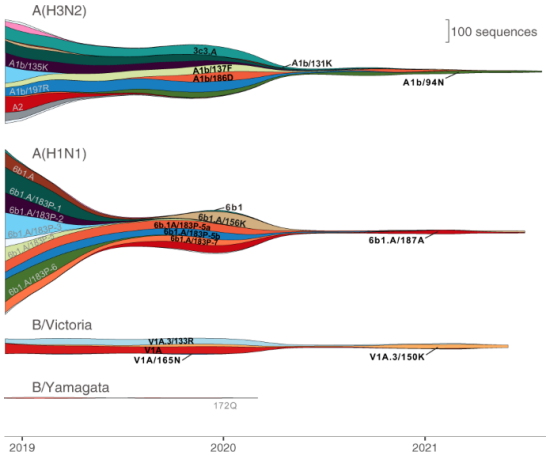
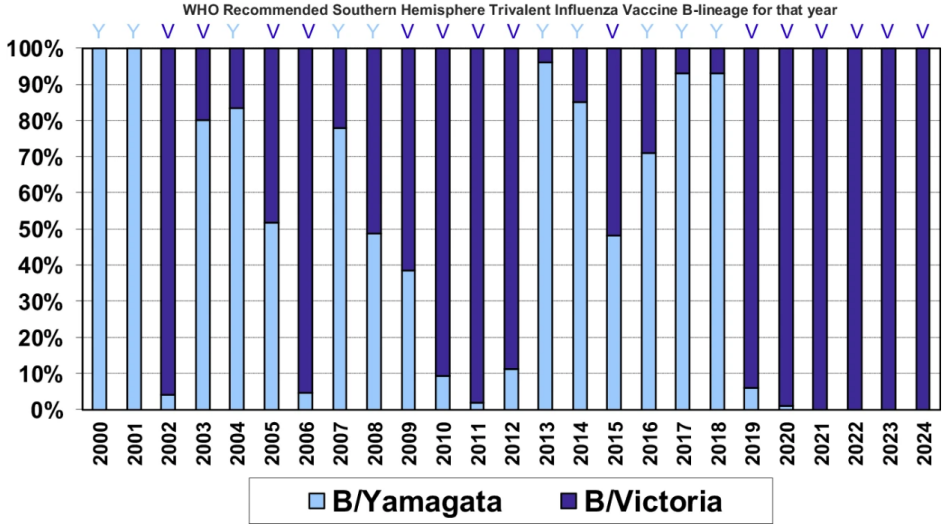
Influenza lineage circulation, 2000-2024

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





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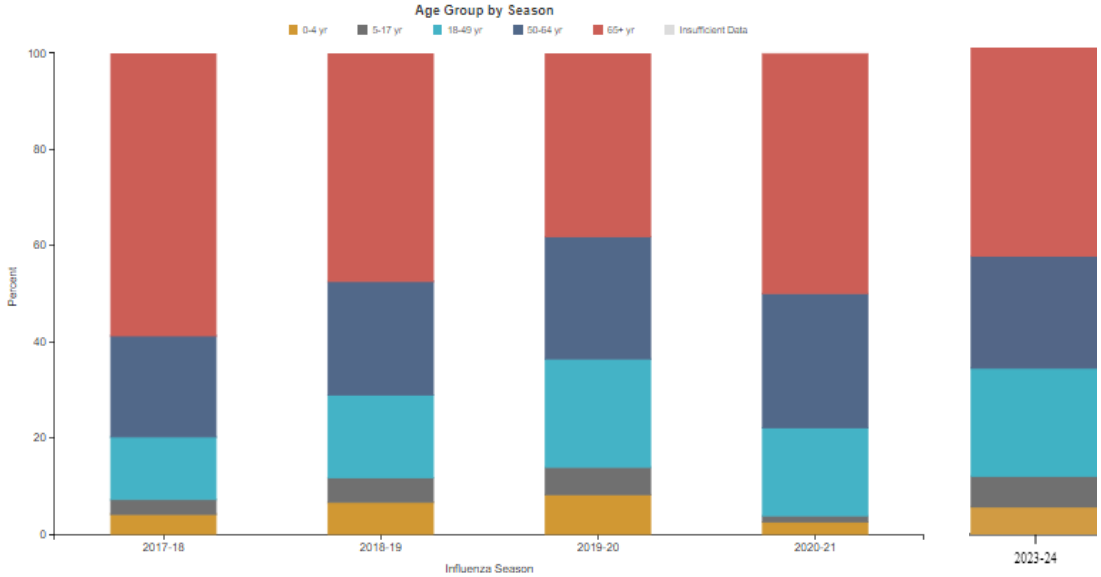
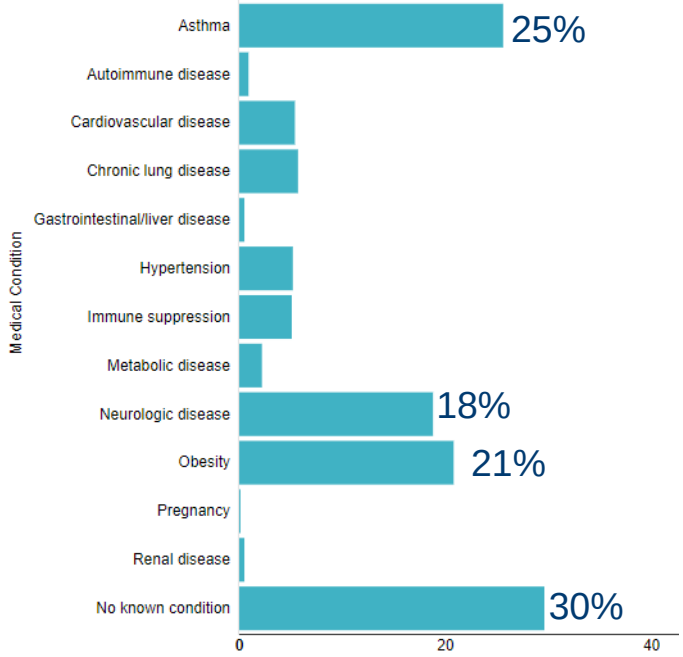
Dhanasekaran V et al. Nature Communications 13, 1721 (2022)
Barr et al. NPJ Vaccines 219 (2024)

Influenza hospitalizations



Medical conditions among children hospitalized in 2023-24



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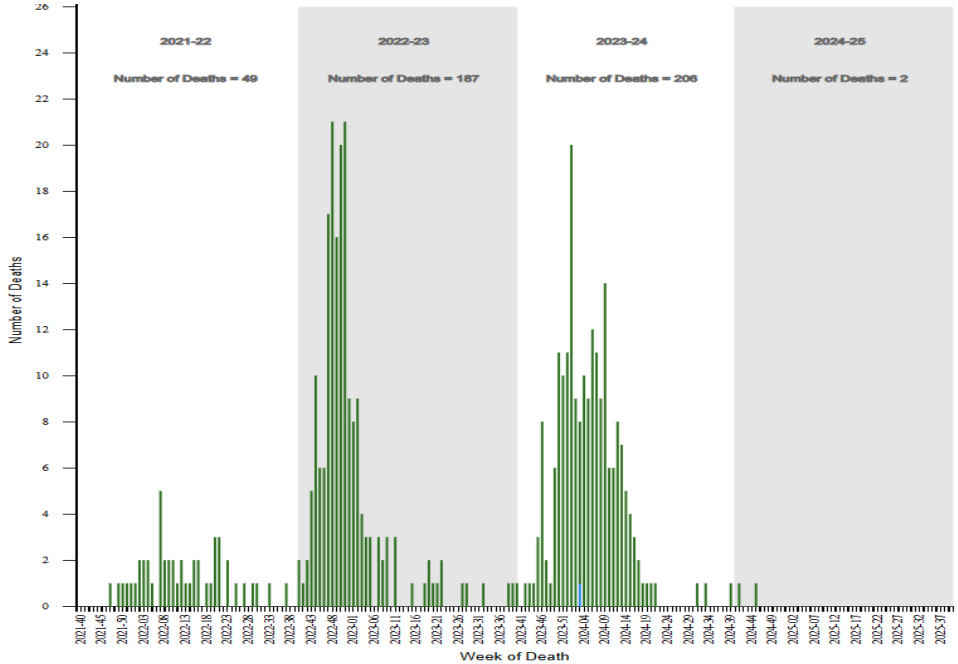
https://www.cdc.gov/flu/weekly/index.htm

Pediatric Influenza mortality over 4 seasons



49% had pre-existing medical condition

Among those with known vaccination status, 83% not vaccinated

Cause of death in children:
Respiratory Failure
Primary or secondary pneumonia, sepsis/SIRS
Severe dehydration
Myocarditis
Neurologic complications

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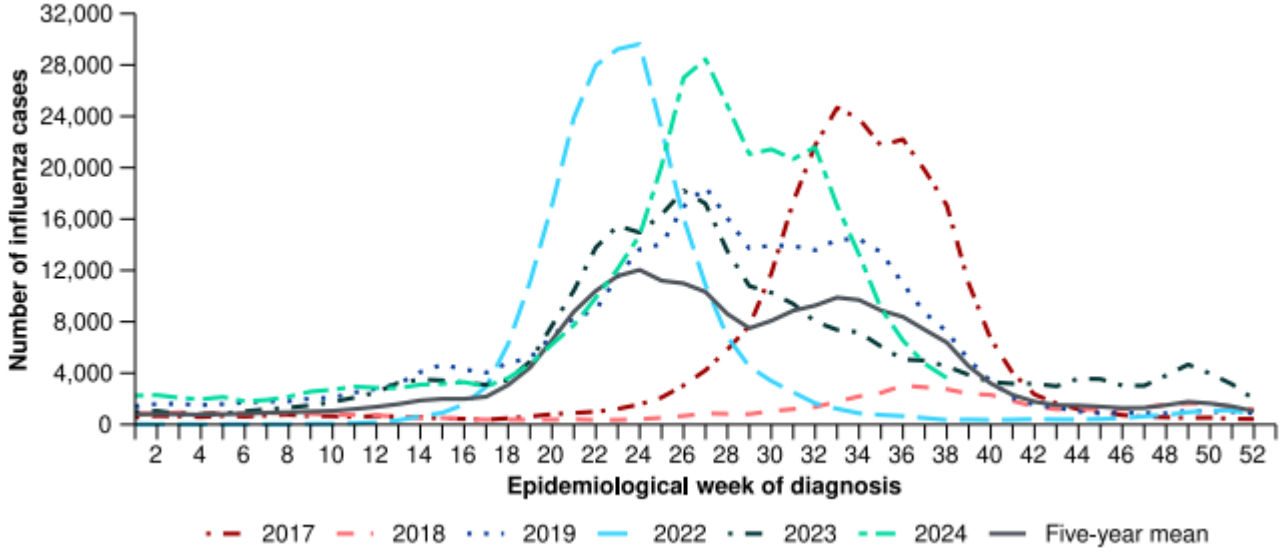
https://www.cdc.gov/flu/weekly/index.htm

2024 Influenza season cases- Australia



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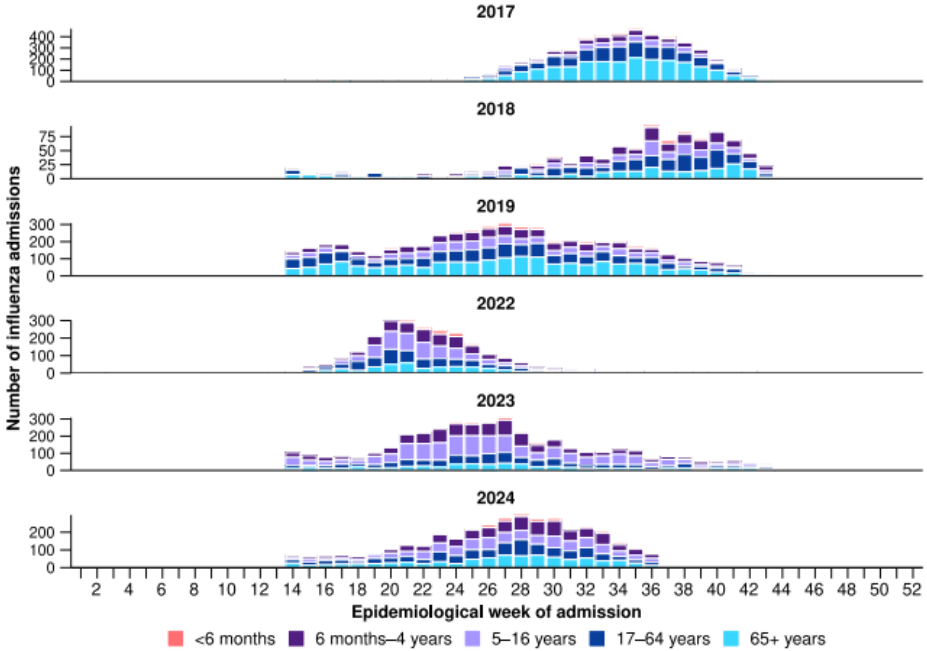
https://www.health.gov.au/sites/default/files/2024-09/australian-respiratory-surveillance-report-13-9-september-to-22-september-2024.pdf

2024 Influenza season- hospitalizations by age



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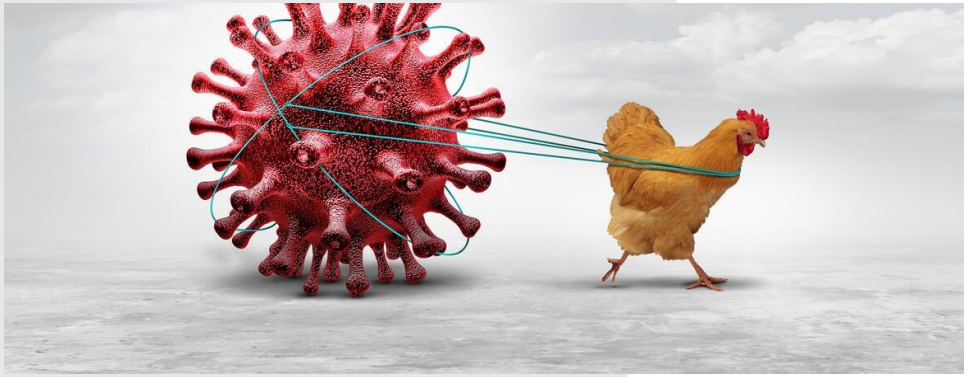


Pandemic potential

Dogs, cats, skunks, bears, seals, porpoises, cows, poultry, birds, ferrets, sea lions, goats, racoons

H5N1- a timeline

1997	1997-2002	2003-2023	April 2022	March 2024	April 2024	May 2024	June 2024
Fatal respiratory disease developed in a child in Hong Kong	Culling poultry, cleaning, and monitoring the live-bird markets in Hong Kong eliminated new human cases of H5N1	Re-emerged, with 900 human infections reported in 23 countries over 20 years	Case 1 in Colorado while culling poultry	Detected in un-pasteurized milk isolated from sick dairy cows in the United States	Case 2 first human infection in a worker exposed to dairy cattle was reported in Texas	Cases 3 and 4 in workers exposed to dairy cattle in Michigan	Case 5 in worker exposed to infected dairy in NE Colorado

H5N1- a timeline

Four poultry workers diagnosed with H5N1 in NE CO (fever, chills, coughing, sore throat and runny nose)

Additional cases from exposure to poultry and dairy cows

Case in Missouri, no clear source identified, closely related to cow virus strains

2 H5N1 cases in farm workers in Central Valley, California

Child in Canada, initially developed conjunctivitis, URI sx, critically ill, no animal exposure

Child in California mild sx, no animal exposure, drank raw milk, routine surveillance

Department of Agriculture issued a federal order requiring the testing of the nation's milk supply

Case 2

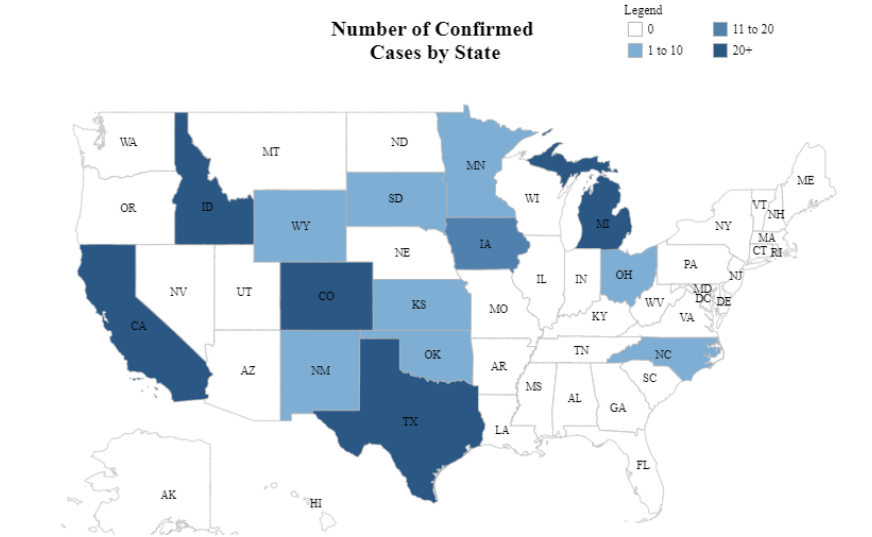
- Texas dairy farmer
- Right eye conjunctivitis (subconjunctival hemorrhage and thin, serous drainage)
- No contact with sick or dead birds, but contact with healthy and cows with similar symptoms as cows in other dairy farms with confirmed H5N1 (decreased milk production, reduced appetite, lethargy, fever, and dehydration)
- Wore gloves but not respiratory or eye protection
- Nasopharyngeal and conjunctival swabs positive for H5N1 via PCR testing
- Subsequently developed redness in his left eye
- (Predominance of α2,3-linked sialic acid (SA) on the ocular surface- H5 and H7 preferentially bind)
- Recovered over the following days, and no symptoms were reported in his contacts
- Sequencing- same B3.13 genotype circulating in dairy cows
- PB2 E67K mutation that has a known link to virus adaptation to mammalian hosts

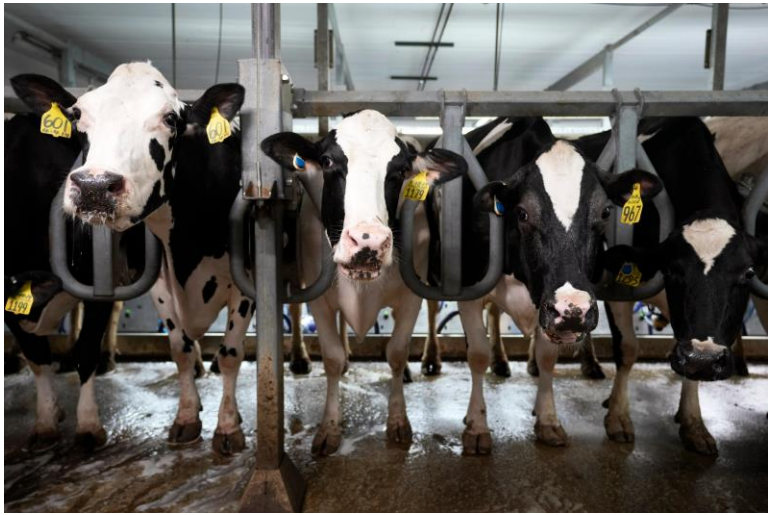
Uyeki et al. NEJM 2024; 390:2028-2029

Colorado has the most cases of bird flu among dairy cows in the U.S.

By John Daley · Jul. 2, 2024, 5:14 pm

Confirmed Cases Total Outbreak	States Affected Total Outbreak
283	14





https://www.aphis.usda.gov/livestock-poultry-disease/avian/avian-influenza/hpai-detections/hpai-confirmed-cases-livestock

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H5N1- what pediatric community should know

14 States with outbreaks in cattle, 48 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

H5N1- what pediatric community should know

12 States with outbreaks in cattle, 48 states with outbreaks in poultry

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Closely related to two existing HPAI A(H5N1) candidate vaccine viruses

Avoid consuming unpasteurized milk and products

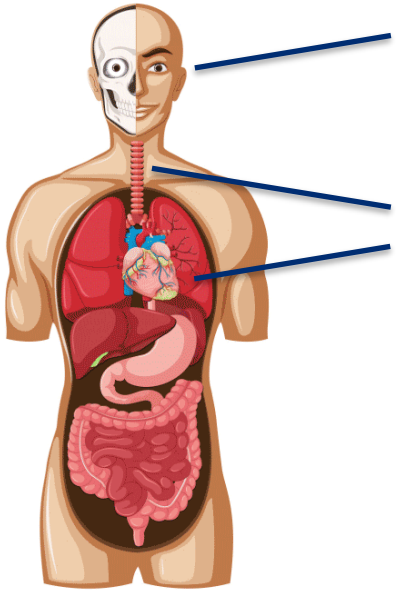
Cook poultry, eggs, and beef to a safe internal temperature

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

PCR-based testing if respiratory symptoms and or conjunctivitis if exposure– (will be not subtypeable, sent to health department for testing

Concerns with current H5N1 outbreak in cattle

- Bovine HPAI H5N1 virus bound to sialic acids expressed in human upper airways
- Fatal HPAI H5N1 virus infections of cats on affected farms
- Inefficiently transmitted to exposed ferrets, transmission to mice resulted in death with virus observed in lung, brain and nasal turbinate
- Cow-H5N1 virus bound to both α2,3- and α2,6-linked sialic acids (not observed from prior avian isolates)



Ref: Eisfeld et al. Nature July 8, 2024
Photo from Google images

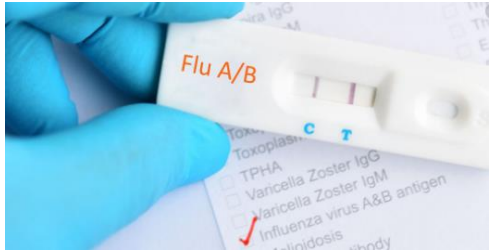
Influenza testing

Whom to test depends on how results will affect clinical management

- Turnaround time of tests
- Patient's illness severity
- Disease prevalence
- Availability of other ancillary test results
- Co-morbidities, risk factors
- Public health and infection control considerations
- Duration of symptoms
- Types of testing available

Hanson et al CID 2020
Rao S. Curr Opin Infect Dis. 2014 Aug;27(4):342-7

Testing



Point of care tests

PCR NAAT DIA RIDT

Decreasing sensitivity

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Source: Google images

Main testing takeaways

- Traditional RIDTs being phased out -poor sensitivity
- RIDTs now need to demonstrate sensitivity and specificity of at least 80%
- RIDTs have higher sensitivity and specificity in children (higher viral loads)
- DIAs are simple, fast and more reliable than RIDTs, but NAAT have highest sensitivity, specificity (90-95%)
- Can diagnose influenza on the basis of a positive RIDT, DIA, or rapid NAAT result during influenza season, less reliable outside season
- Newer SARS-CoV-2/influenza/RSV tests are replacing other tests in office settings

At home testing

$30 to $389

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Source: Amazon.com

At home testing

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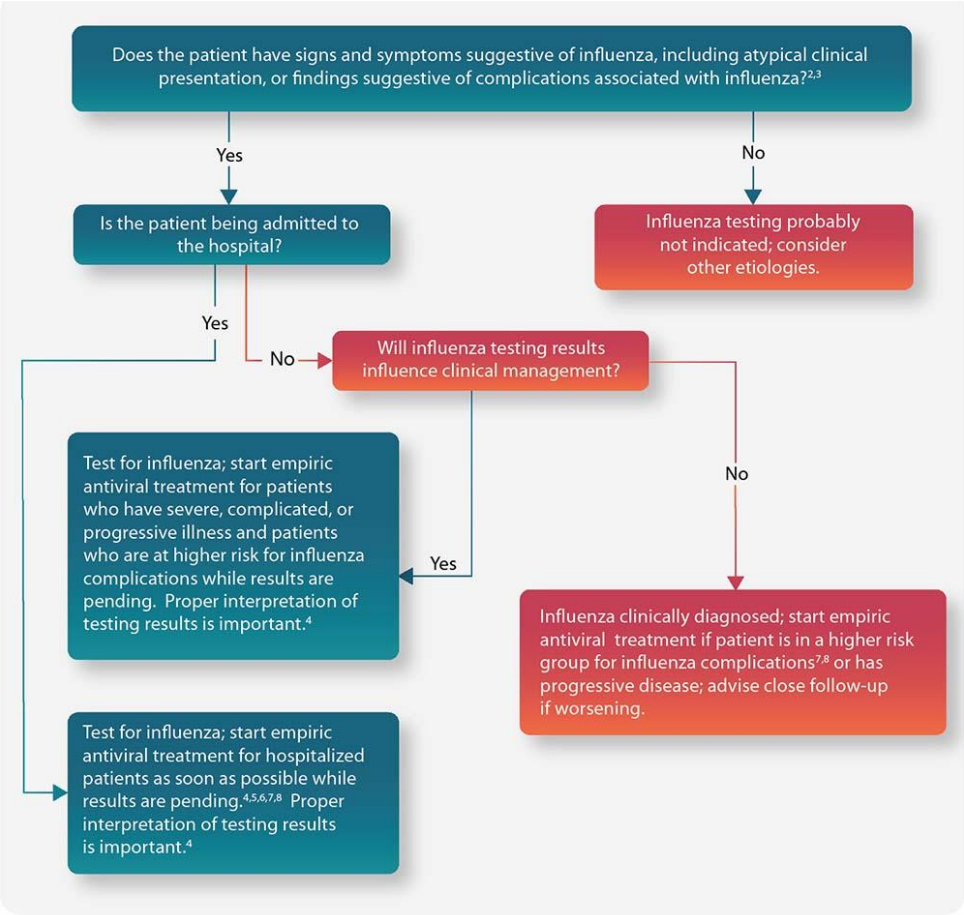
Influenza treatment

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

CDC Testing and treatment guidance



Source: CDC

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

Influenza Treatment

oseltamivir

zanamivir

peramivir

baloxavir

Influenza Treatment

oseltamivir

14 d-3 mo 3 mg/kg/dose bid X 5 days

3-12 months: 3 mg/kg/dose bid

Children 1-12 years:

≤ 15 kg: 30 mg/dose bid

> 15-23 kg: 45 mg/dose bid

>23-40 kg: 60 mg/dose bid

>40 kg: 75 mg/dose bid

Children > 13 years and adults:

75 mg/dose bid

SE: nausea, vomiting, behavioral change

zanamivir

Two inhalations (10 mg) twice daily X 5 days

7 years of age and older

Not recommended in patients with underlying airway disease due to risk of bronchospasm. Contraindicated in those with milk-protein allergy

peramivir

Children 6 months-12 years: 12 mg/kg once daily IV

13 years and older: 600 mg once daily IV

Treat for 5-10 days (ID consult)

Monitor renal function

Diarrhea, behavioral changes, neutropenia

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

baloxavir

Children 5 years of age and older:

<20kg: 2mg/kg as a single dose using the suspension formulation

20 to <80 kg: 40 mg as a single dose

>80 kg: 80 mg as a single dose

Well tolerated

Avoid administration with dairy, calcium fortified drinks or polyvalent cations

Treatment – how effective are antivirals?

Cochrane review – 6 RCT (2356 children) and 5 new RCTs (1598 children)

Oseltamivir can decrease illness duration by 1.5 days, zanamivir by 1.3 days

Oseltamivir can decrease risk of acute otitis media in children 1-5 yrs

Reduction in influenza-associated deaths

If given within 48 hrs of illness onset, aOR 0.37; 95% CI, 0.22 to 0.63
If given within 5 days, of illness onset, aOR 0.5; 95% CI, 0.32 to 0.79

Reduction in transmission

If given within 48 hrs of illness onset, reduced viral shedding (12% vs 6%, p = 0.0009)

Wang K et al. Cochrane Database Syst Rev. 2012;(4):CD002744;
Jefferson T, et al.. Cochrane Database Syst Rev. 2014;(4):CD008965;
Domínguez A et al. Epidemiol Infect. 2018;146(7):799–808
Hayden et al. CID July 10 2021; Fry et al. Lancet Infectious Diseases 14 (2) P109-118

PHIS data- hospitalized children

Coffin et al.
If given within 24 hrs of hospitalization, 18% reduction in total hospital days (Time Ratio: 0.82, p=0.02)

Miyakawa et al.
Children with tracheostomy LOS 6.4 days vs 7.5 days (p = 0.01)

Walsh et al.
Shorter hospital stay and lower odds of 7-day readmission, transfer to the intensive care unit, and in-hospital mortality or use of extracorporeal membrane oxygenation

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Coffin SE et al. Pediatr Infect Dis J. 2011;30(11):962-6
Miyakawa R et al. Pediatrics. 2019;143(3):e20182608 35
Walsh PS et al.JAMA Pediatr. 2022;176(11):e223261

Misclassification Influenza Infection and Oseltamivir in Administrative Data

- Study conducted at 3 hospitals participating in PHIS
- Reviewed children coded as influenza using similar sampling criteria to Walsh et al.
- Reviewed 100 medical records
- Evaluated % inaccurately classified as hospitalized for influenza and did not receive but should have received oseltamivir
- Among 300 patients, 188 (63%) were inaccurately classified, did not have influenza (n = 118), or they received oseltamivir prior to hospitalization (n = 34)
- Median (IQR) LOS was longer in patients who were inaccurately vs accurately classified
- (i.e. those classified as hospitalized for influenza but not receiving oseltamivir do not represent the true unexposed population of interest)

Bassett et al. JAMA Pediatrics February 2024; 178 (2): 201-203

Influenza vaccination

ACIP updates, 2024

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

All influenza vaccines marketed in the US will be trivalent (no Yamagata)

Egg-based vaccines
- A/Victoria/4897/2022 (H1N1)pdm09-like virus;
- A/Thailand/8/2022 (H3N2)-like virus;
- B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

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• B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

High-dose inactivated (HD-IIV3) and adjuvanted inactivated (aIIV3) influenza vaccines for solid organ transplant recipients aged 18 - 64 years who are on immunosuppressive medication regimens, no preference

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Source: ACIP Presentation Grohskopf L. 27 June 2024. WG Considerations and Proposed Recommendations.

AAP and CDC influenza vaccine recommendations

Indicated for pediatric population

* Afluria 6-36 months 0.25 mL dosing, all others 0.5 mL

Any licensed vaccine appropriate by age, no product preference

Can be administered at the same time as COVID-19 vaccines

Administration at any healthcare seeking visit

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

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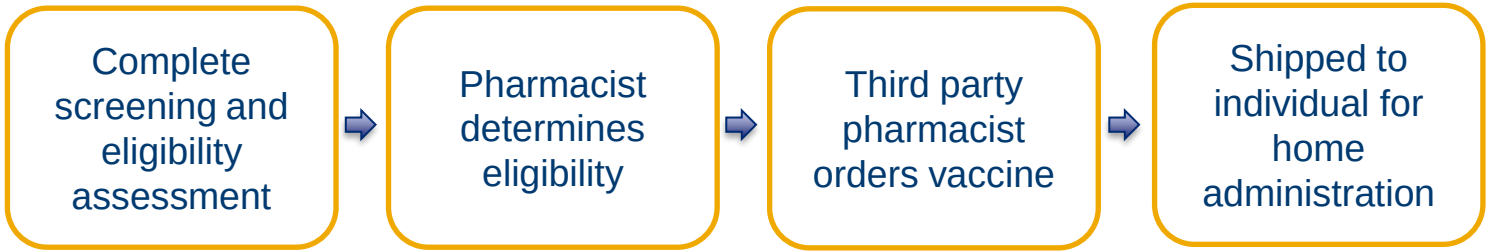
Live attenuated influenza vaccine at home administration

FDA approved home administration in September 2024

Ages 2-49 years

Home delivery anticipated for 2025-26 season

Will be available through third-party online pharmacy



Contraindications and Precautions

	Contraindications	Precautions
IIV	Severe allergic reaction to any component of vaccine	GBS within 6 weeks of prior influenza vaccine
LAIV	Severe allergic reaction to any component of vaccine Receiving aspirin therapy < 5 years of age with recurrent wheezing Immunosuppression CSF leak/active communication, cochlear implant Concurrent antiviral use	Asthma GBS within 6 weeks of prior influenza vaccine Underlying high risk conditions

* Conditions for which there is either uncertain but biologically plausible potential risk associated with live viruses or limited data for use of LAIV

Grohskopf LA et al. MMWR 2024 / 73(5);1–25

How effective is the influenza vaccine? 2022-2023 data

	Influenza positive		Influenza negative[1]		Adjusted[2]	
	N vaccinated /Total	(%)	N vaccinated /Total	(%)	VE %	95% CI
Influenza A All 6 mos – 17 years	123/640	19	750/2256	33	**49**	(36 to 60)
Inpatient	19/131	15	288/913	32	**68**	(46 to 81)
ED	104/507	21	461/1330	35	**42**	(25 to 56)
A/H3N2	98/478	21	750/2256	33	**45**	(29 to 58)
A/H1N1pdm09	23/139	17	750/2256	33	**56**	(28 to 72)

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Source: NVSN
Vaccine effectiveness against laboratory confirmed influenza A in inpatient and emergency department (ED) settings, September 13, 2022-January 25, 2023

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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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Interim Estimates of 2023–24 influenza VE

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

	Outpatient visits	Hospitalization	All settings
6 months to 17 years, all influenza	59-67%	52-61%	-
6 months to 17 years, influenza A	46% to 59%	46% to 56%	46% to 59%
6 months to 17 years, influenza B	64% to 89%	-	
> 18 years, all influenza	33-49%	41-44%	
> 18 years, influenza A	27% to 46%	40% to 42%	27% to 46%
> 18 years, influenza B	78%	60%	60% to 78%

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Frutos AM et al. MMWR Feb 29, 2024/73(8): 168-174

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6 months to 17 years, influenza B	64% to 89%	-	
> 18 years, all influenza	33-49%	41-44%	
> 18 years, influenza A	27% to 46%	40% to 42%	27% to 46%
> 18 years, influenza B	78%	60%	60% to 78%

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Frutos AM et al. MMWR Feb 29, 2024/73(8): 168-174

Decreased risk of hospitalization, death and ICU admission

- Influenza vaccination can decrease your risk of being hospitalized by 68%

- Influenza vaccination can decrease the risk of a child being admitted to the ICU by 74%, and an adult by 82%

- Influenza vaccination can decrease a child's risk of dying from the flu by 65%

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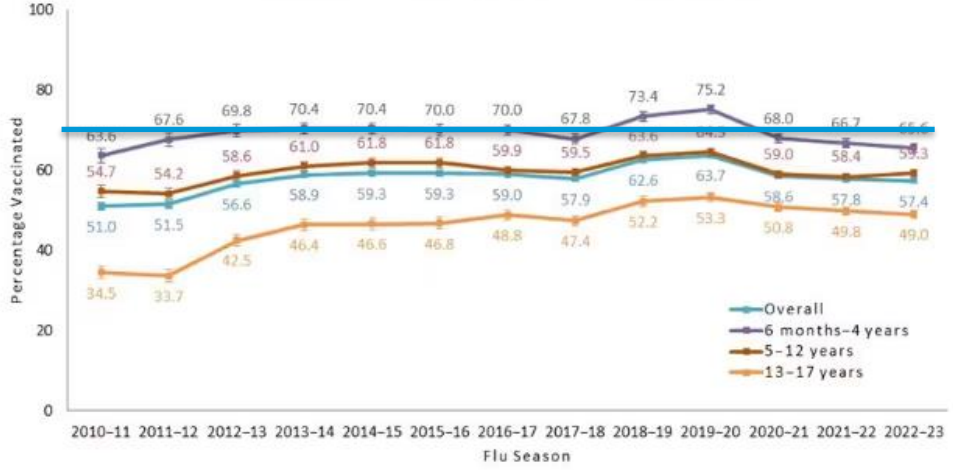
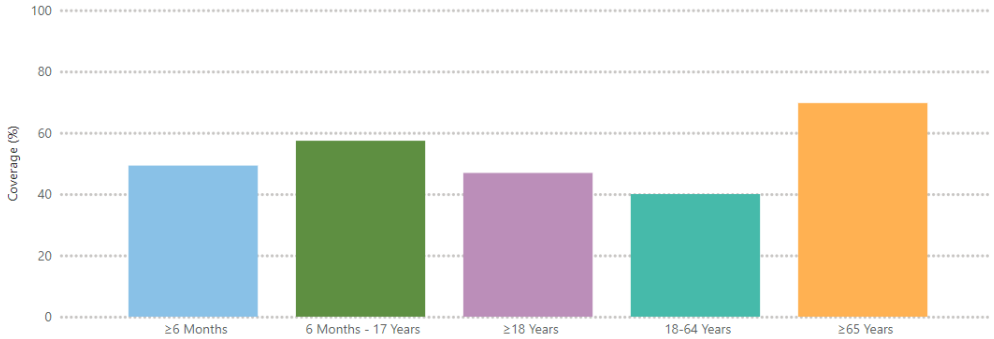
Flannery et al. Pediatrics May 2017, 139 (5) e20164244
Feldstein JPIDS 2020; Segaloff CID 2019 69(12):2153-2161; Blyth et al. Vaccine 2020;38(13):2779–2787;
Kaalligeros M et al. Vaccine 2020;38(14):2893–2903

Influenza vaccine uptake





Healthy 2030 goal 70%

Coverage is
9-10% points lower than pre-pandemic coverage

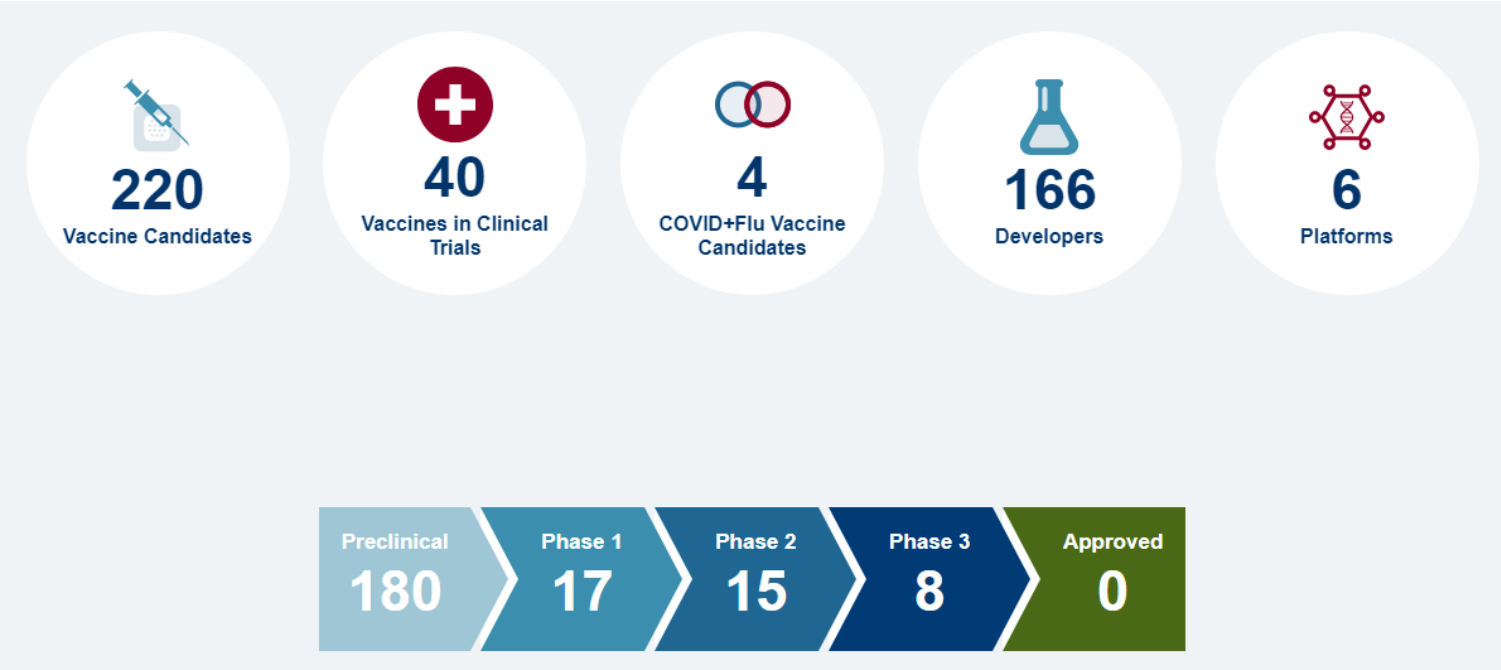
Lower among children in rural areas, Hispanic and black/African American children

https://www.cdc.gov/flu/fluvaxview/coverage-2223estimates.htm

New vaccines in development

Influenza virus-based | **Nucleic acid-based** | **Non-VLP nanoparticles**

Virus-vectored | **Recombinant proteins** | **VLP nanoparticles**



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

Main takeaway points

Influenza back to pre-COVID pandemic levels

H5N1 transmission in birds, cows and other mammals, no human-human transmission currently

RIDT improved manufacturing standards, NAAT have highest sensitivity and specificity and are now available for at home testing

Influenza treatment – reserve for hospitalized and those at high risk

Focus messaging on preventing severe disease, vaccine uptake declining since COVID-19 pandemic

Questions?