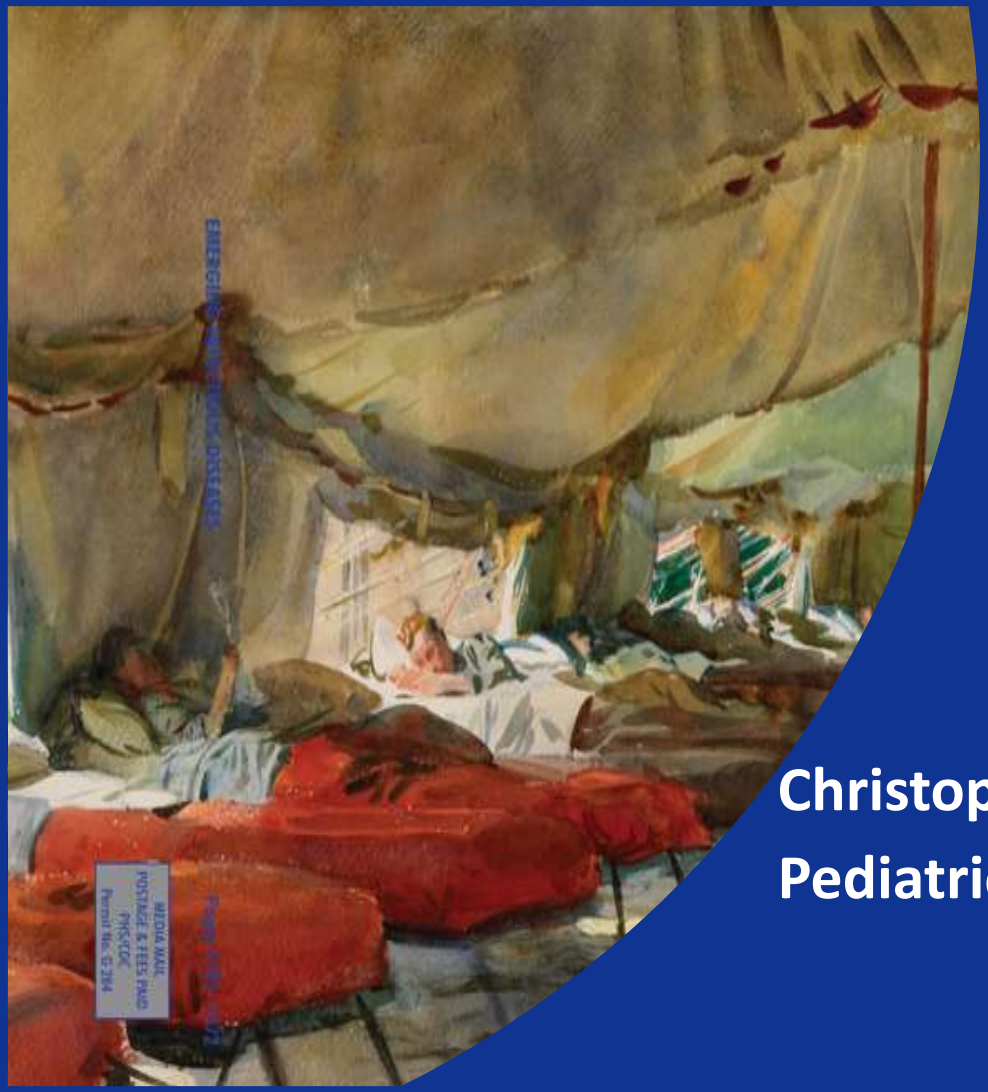

Update on Influenza 2018-19

Christopher J Harrison MD, FAAP, FPIDS
Pediatric Infectious Diseases

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Plan

- How was last flu season?
  - Nationally and locally
  - Pediatric risk groups
- What makes flu dangerous
- Vaccines for this year
  - LAIV use
- Last year's uptake and places dispensing vaccine
- Waning intra-seasonal protection?
- Kinds of flu vaccine – mostly now and 1 for future
- Pregnancy and flu
- Antivirals
- Effect of humidity on contagion

Severe 2017-18 Season

2017-2018 flu season:

among most severe on record per CDC

- Nov to Apr, peaked in Jan-Feb (19 wks)
- ILI peaked at 7.5%, highest since pandemic (7.7%)

- **80,000 total deaths**
  - **Greater than usual 12,000-56,000 total deaths in flu season** https://www.cdc.gov/flu/about/disease/2015-16.htm
    - **1918 pandemic had 500,000 deaths**
- **Many thousands children hospitalized with influenza**
  - **180 pediatric influenza-associated deaths**
  - **~80% of pediatric deaths unimmunized vs influenza**

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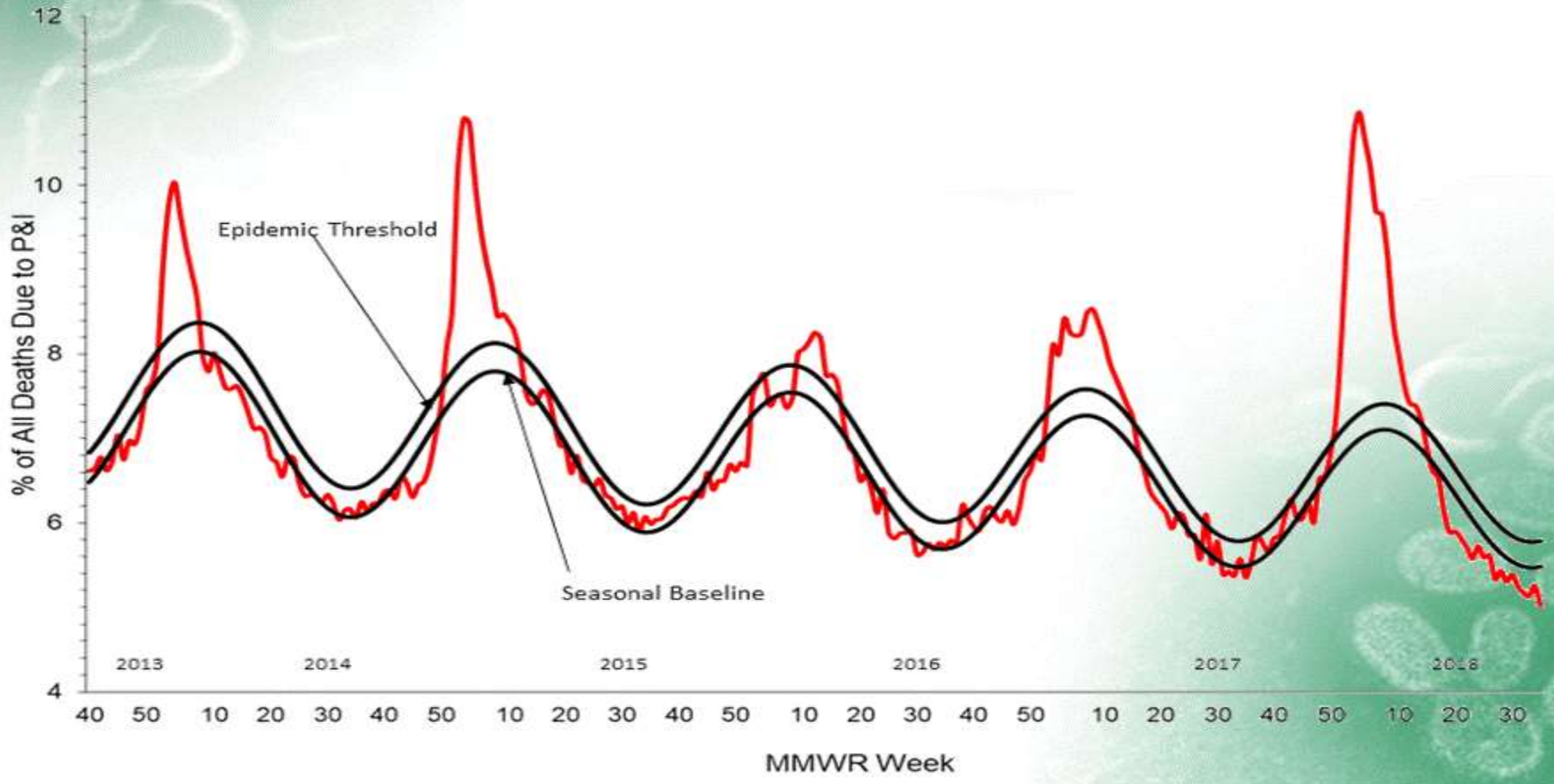
FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

CDC
Centers for Disease Control and Prevention

Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System

Data through the week ending September 1, 2018, as of September 20, 2018



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FLUVIEW

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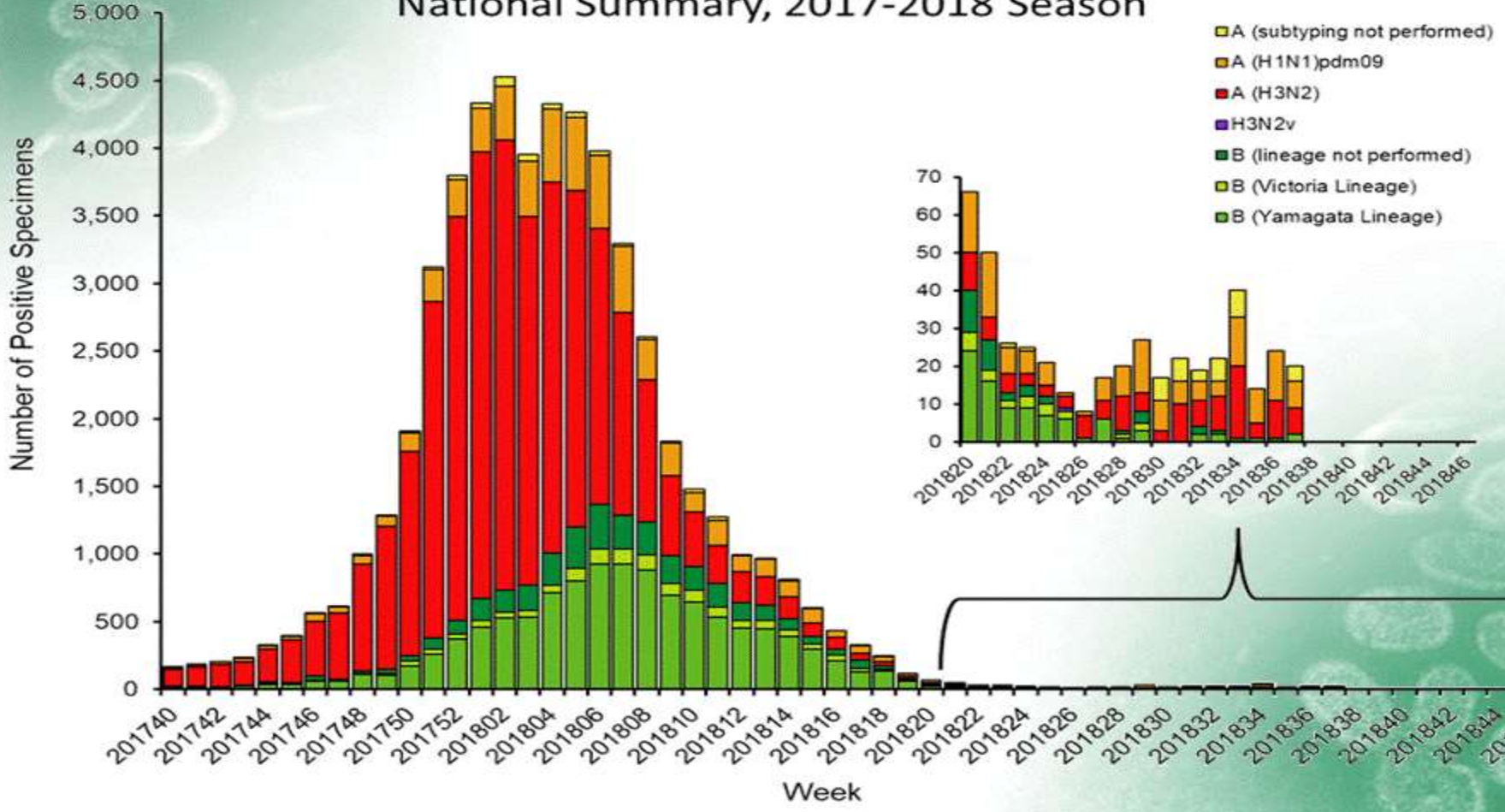
CDC
Centers for Disease Control and Prevention

Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, National Summary, 2017-2018 Season

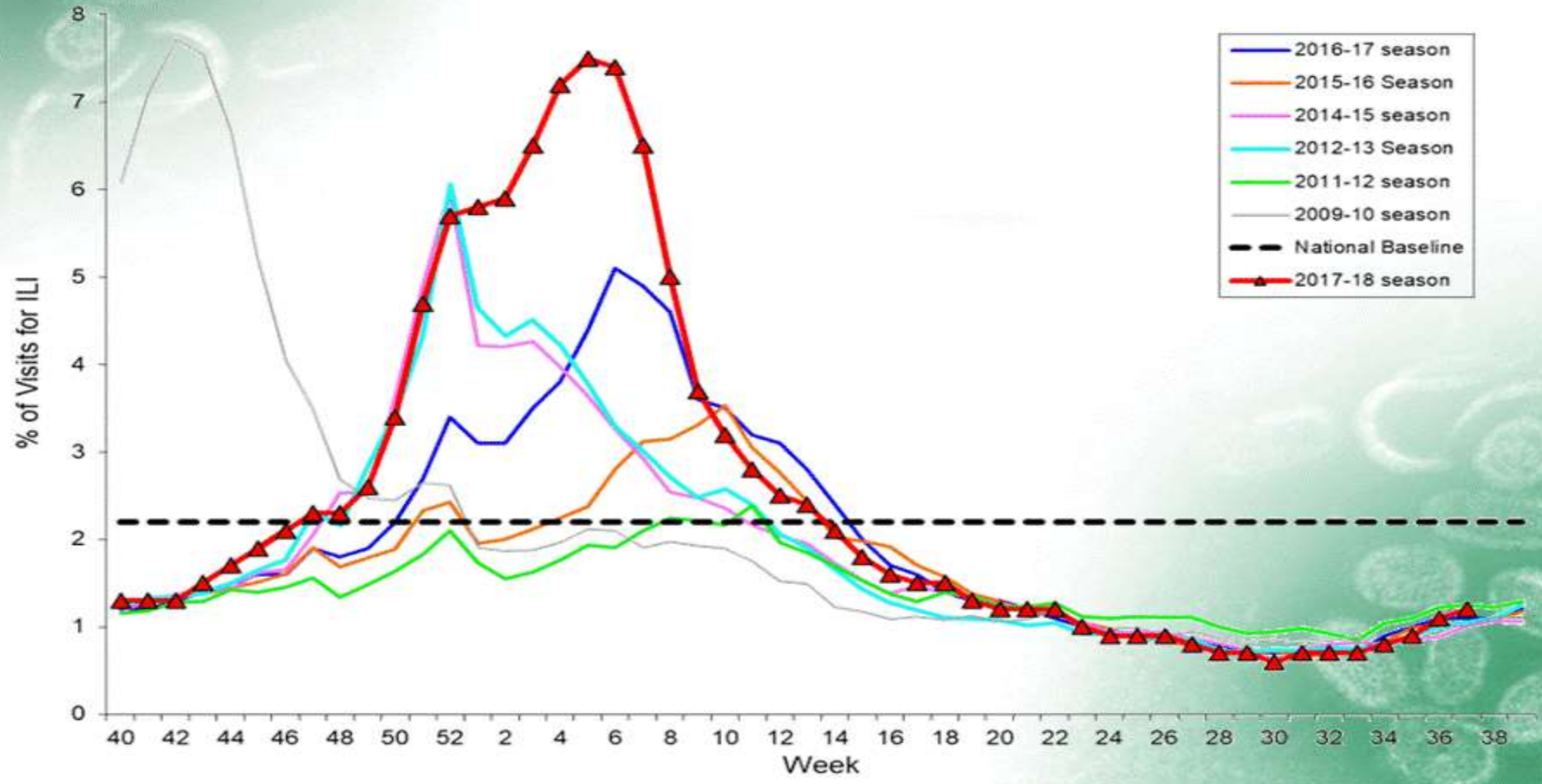


FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

CDC
Centers for Disease Control and Prevention

Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, 2017-2018 and Selected Previous Seasons



Kansas ILI rates 2015-2018

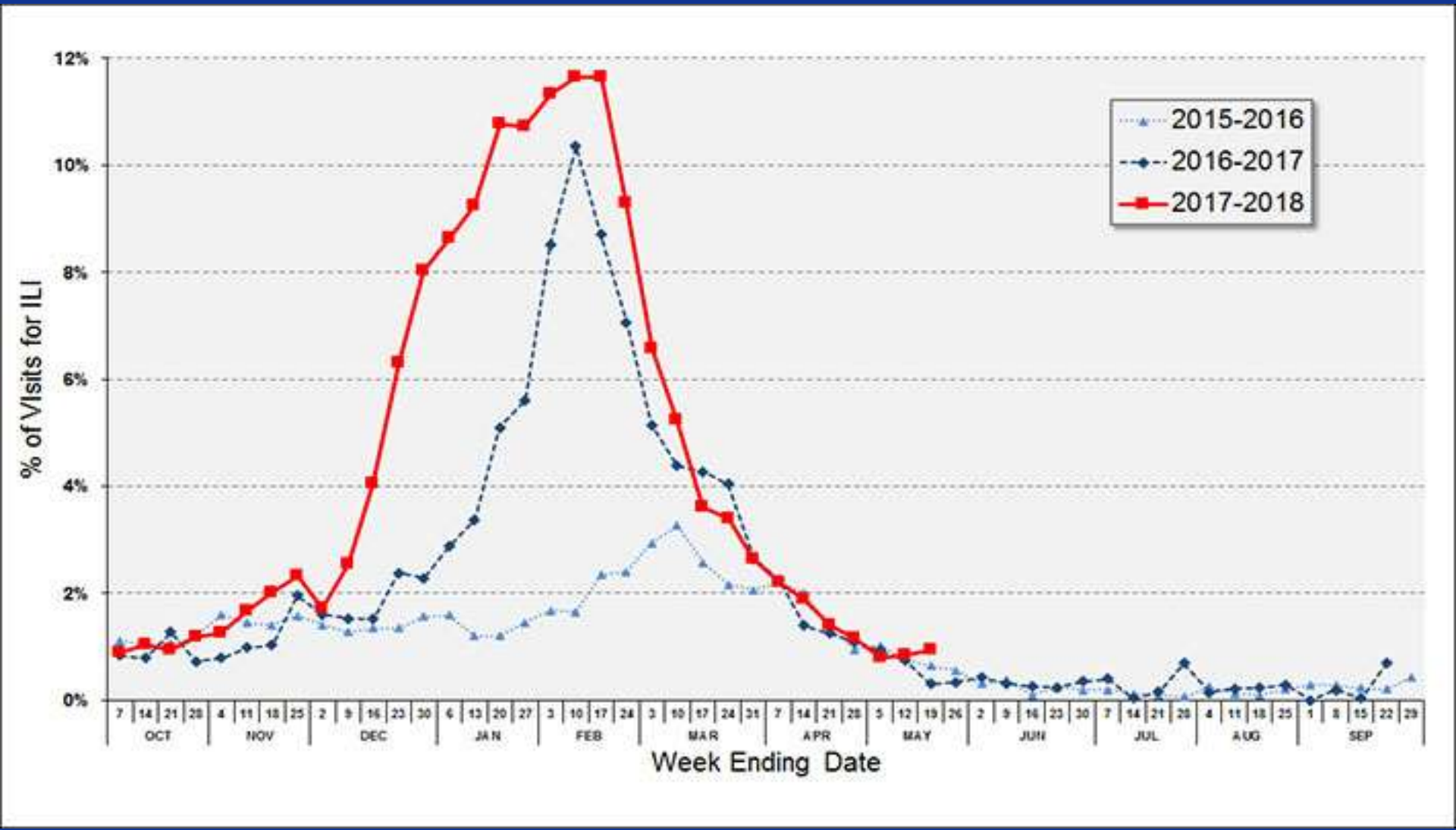
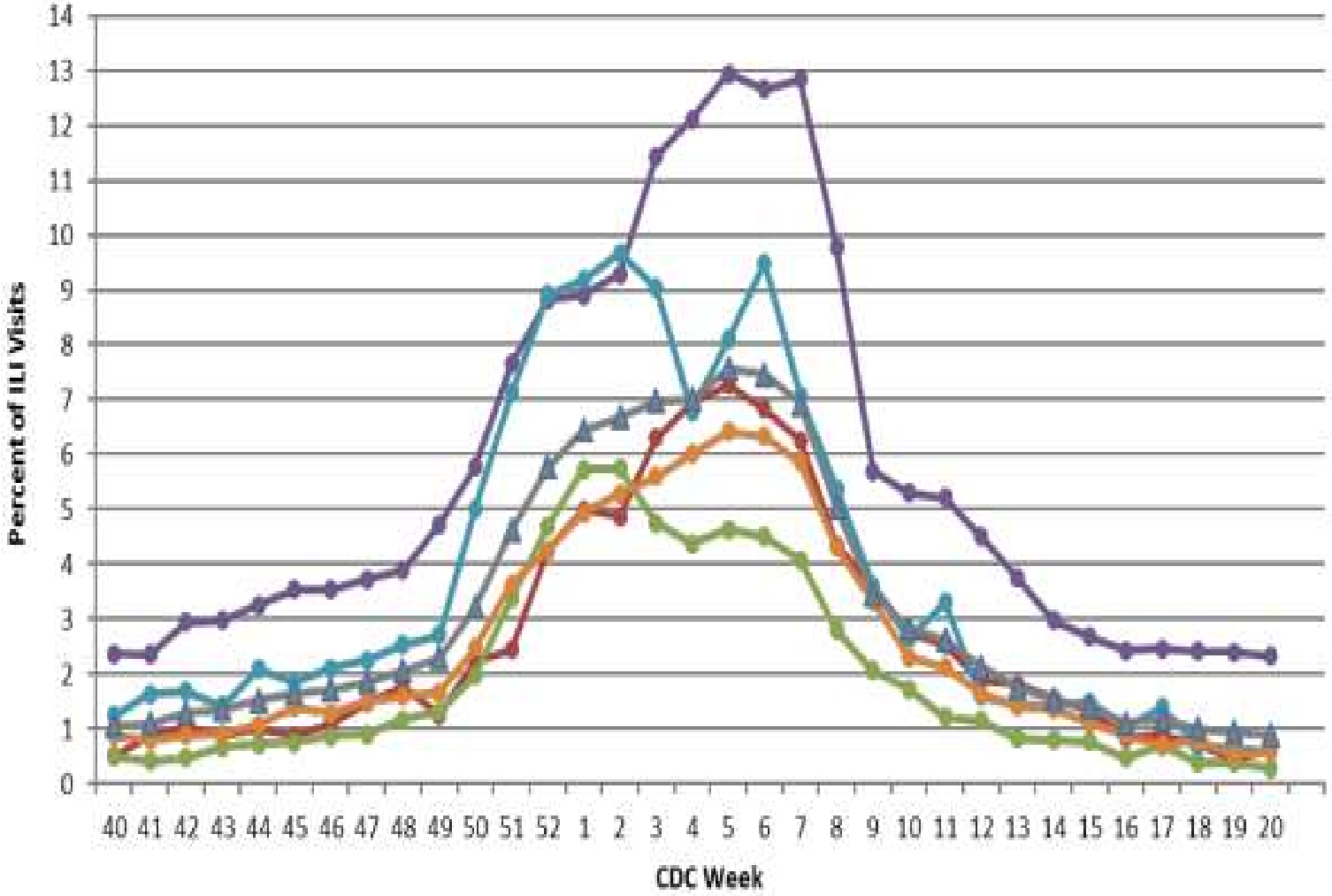
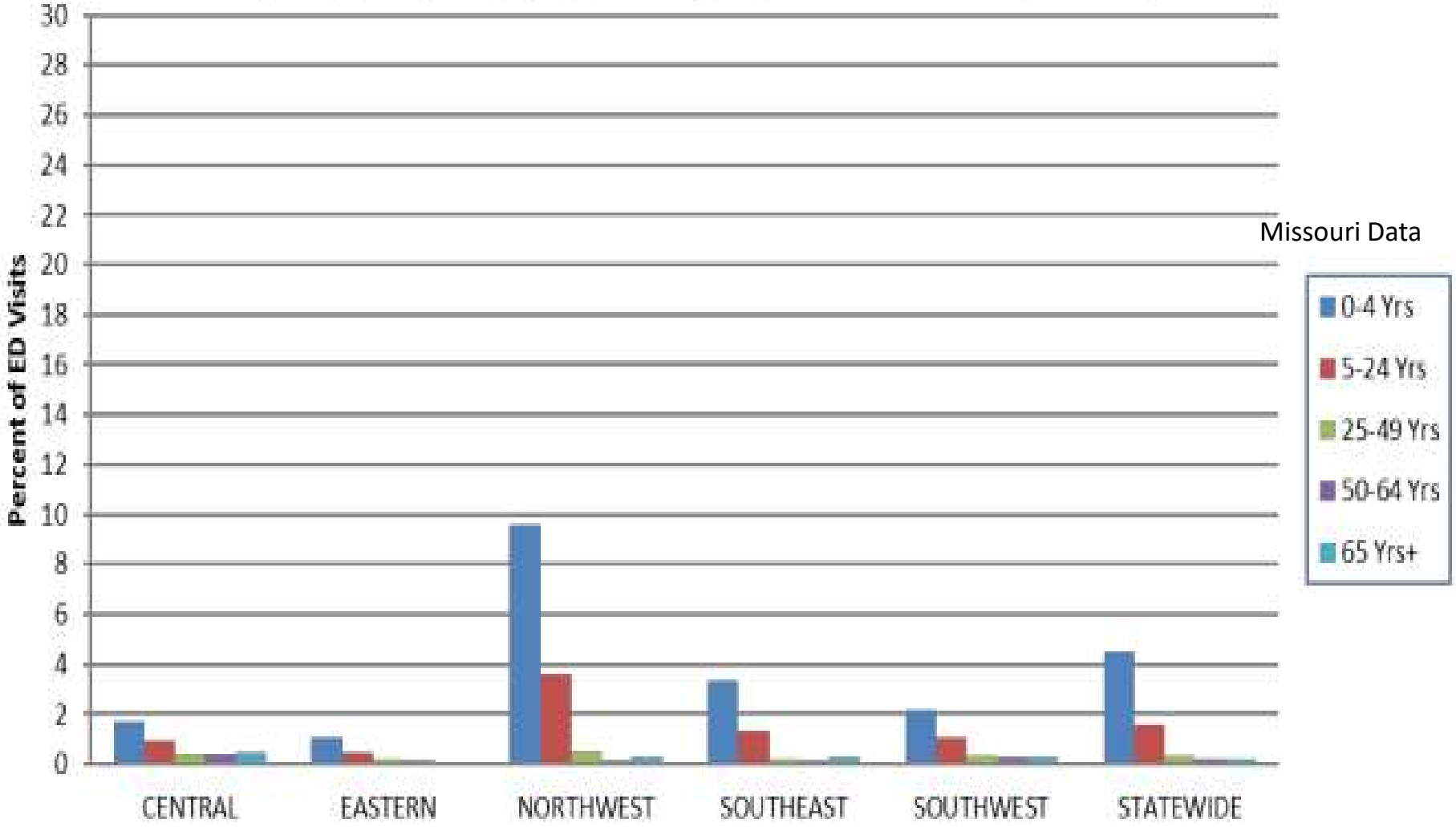


Figure 9. Percentage of Emergency Department (ED) Visits for Influenza-like Illness (ILI) in ESSENCE Participating Hospitals, by Region and Statewide, 2017-2018 Influenza Season*



Missouri Data

Figure 8. Percentage of Emergency Department (ED) Visits for Influenza-like Illness (ILI) in ESSENCE Participating Hospitals, by Age Group, Region and Statewide, Week 20, 2018*

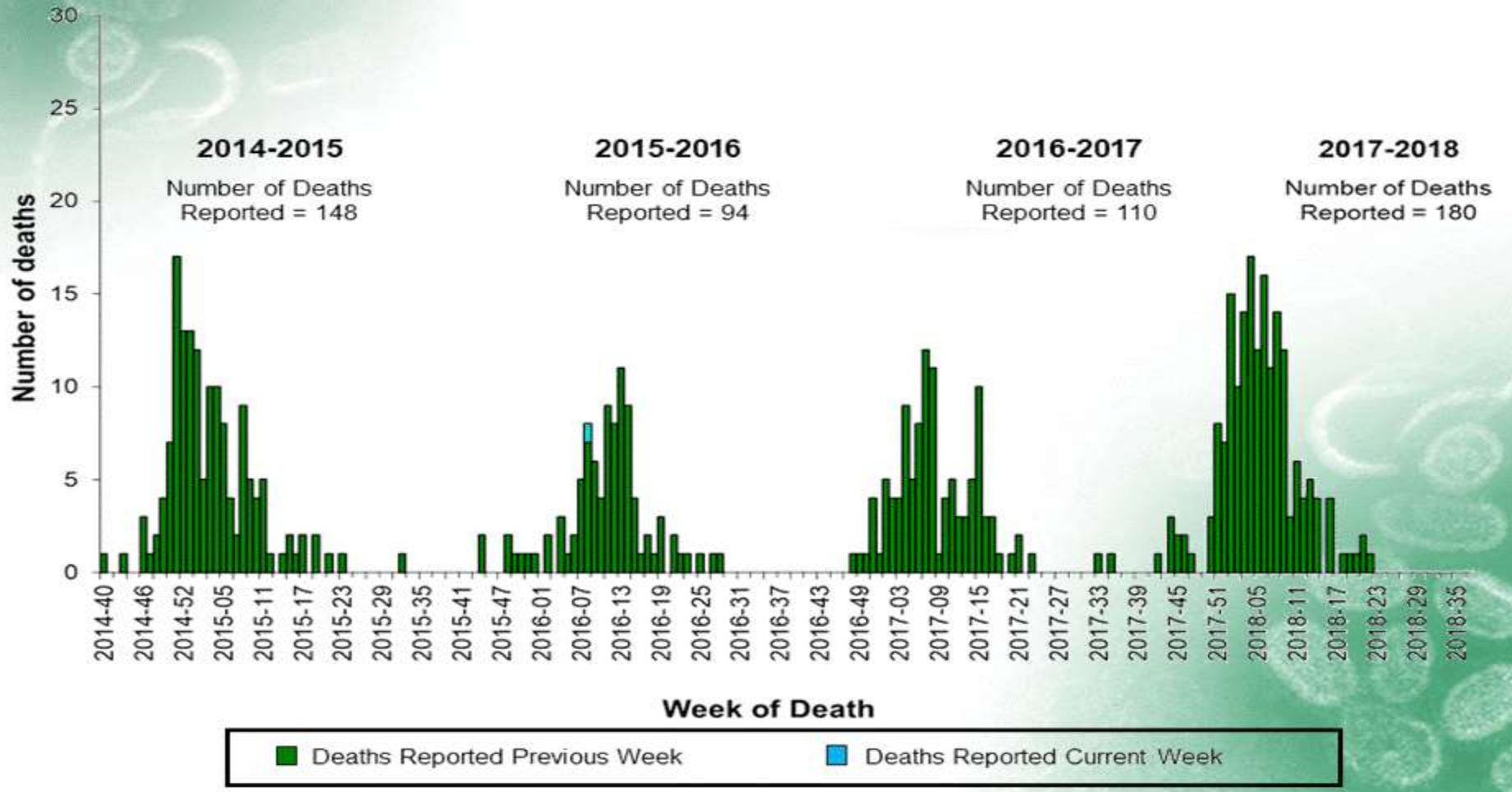


Missouri Data

FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

Number of Influenza-Associated Pediatric Deaths by Week of Death: 2014-2015 season to present

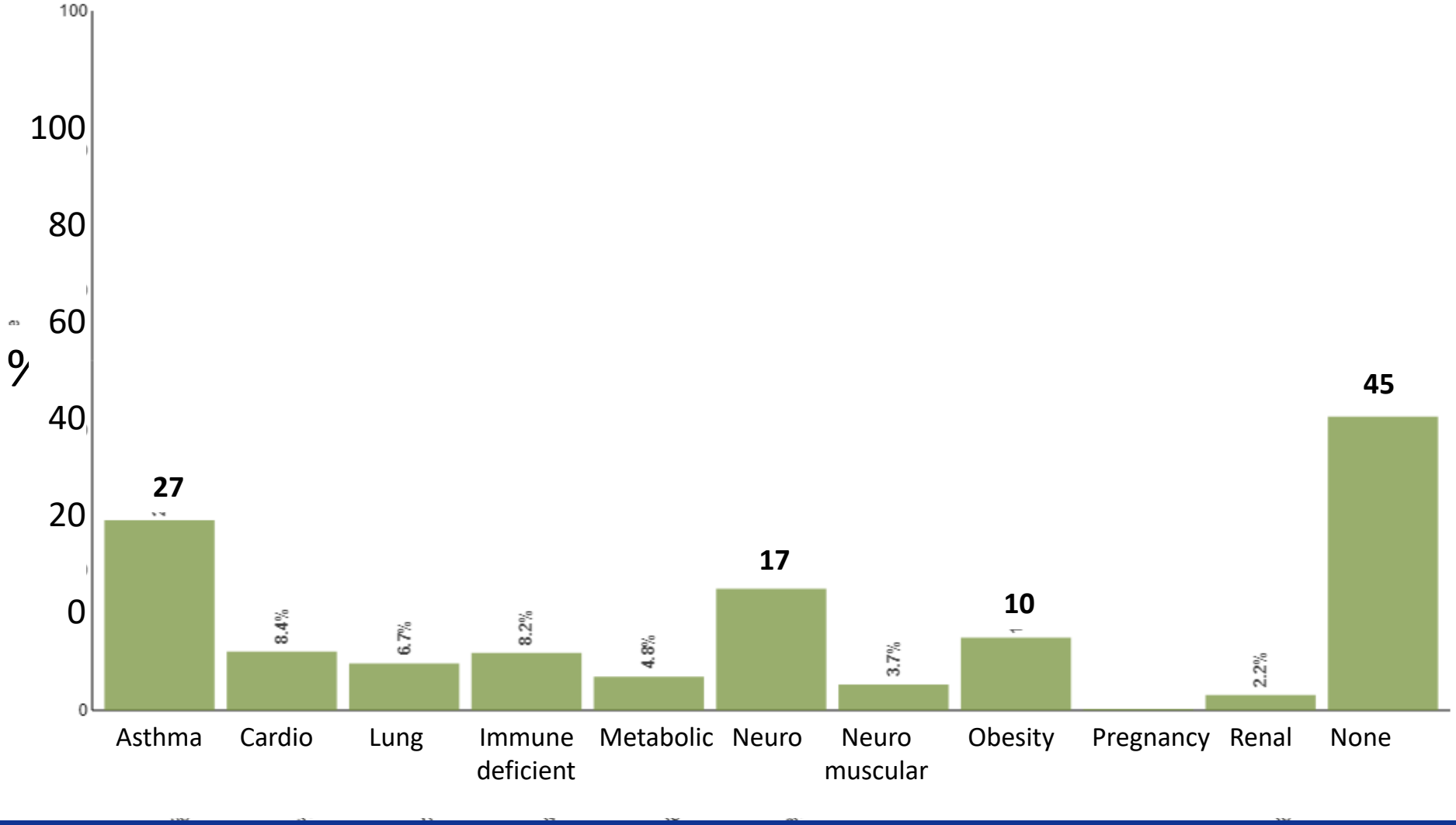


Persons at High Risk forSevere Outcome or Complications from Influenza Infection

- Children <59 mo and adults ≥50 yo
- Women: are/will be pregnant during influenza season
- American Indians/Alaska Natives
- Extremely obese (BMI ≥40)
- <18yo on ASA/salicylate-containing meds (Reye syndrome)
- Chronic lung (asthma too), cardiovascular (not isolated HTN), renal, hepatic, neurologic, hematologic, or metabolic disorders (including DM)
- Immunocompromised - any cause
- Nursing home and long-term care facility residents

Emphasis: Those who live with or care for higher risk patients need vaccine

Risk Factors for Influenza Pediatric Deaths 2017-18



Vaccines can Prevent Death by Influenza

Immune System is the key – Goldilocks phenomenon

- Not too much to produce excess inflammation
- But enough to contain virus and secondary bacterial attacks

1. **Primary viral infection - even in otherwise healthy**
   - Cytokine storm – high viral load + host genetics
   - Severe lung injury
2. **Viral disease increases physiologic load**
   - Chronic/metabolic/immune illness
   - Pregnancy
3. **Secondary bacterial infection –** we can help
   - Caused most deaths in 1917-18 pandemic
   - Pneumococcus – there's another vaccine for this
   - *S. aureus*

Pain with no gain
Influenza as the Set-up Bug

- **Virus-mediated dysfunction of immune effectors, e.g. polys**
  - Compromises local immunity at normally sterile sites
  - Possible leukopenia = poor outcomes of secondary bacterial infection
- **Most secondary bacterial pneumonia assoc w leukocytosis**
  - Preponderance of polys and immature forms
  - Activated neutrophils and macrophages
    - Add to lung inflammation (mediators)
  - Synergizes with bacterial toxins
- **Despite sheets of polys/macrophages in lung**
  - Functional ability needed to clear bacteria altered
  - ⬇ chemotaxis, phagocytosis, and bacterial killing

Other Influenza Factors

- **Highly virulent strains (1918 and 1957, Bird flu strains)**
  - Damage normally protective epithelia
    - Expose extracellular matrix molecules and basement membrane elements to which bacteria adhere
- **Ciliary function compromised**
  - Loss of large areas of cilia
  - Surviving cilia w decreased beat frequency & dyskinesia
- **All strains create dead space and milieu for bacterial growth**
  - Pulmonary function and diffusion capacity diminished
  - Obstruction of small airways
    - Disruption of surfactant
    - Increased mucous plus fibrin and edema fluid
  - Alveoli full of inflammatory cells

2018-19 Vaccines

- IIV3
  - 1st A H1N1: Michigan/45/2015pdm09–like virus
  - 2nd A H3N2–like Singapore/INFIMH-16-0019/2016 (updated)
  - 1st B Colorado/2017-like in Victoria lineage (updated)
- IIV4, RIV4, and LAIV4
  - 2nd B Phuket/2013–like in B/Yamagata lineage
- For adults – HD-IIV3 and a-IIV3 also available
- New lower age limit
  - Afluria Quadrivalent® (IIV4) down to 5 yo
  - Fluarix Quadrivalent® (IIV4) down to 6 mos

AAP Recommendations

- 1st choice – IIV all ≥6mos old, preferably by Oct 31
  - IIV comes as trivalent (IIV3) or quadrivalent (IIV4)
  - Neither formulation preferred over the other
- 2nd choice – (also ACIP) LAIV4 if would otherwise refuse influenza vaccine
  - >2 years old healthy (no underlying condition)
- Vaccine dose # depends on age and vaccine Hx
  - 6mos through 8yo = 2 doses in 1st year being vaccinated
  - ≥9yo need only 1 dose, regardless of prior vaccination Hx

Dosing for 6 through 35 Month Olds

IIVs

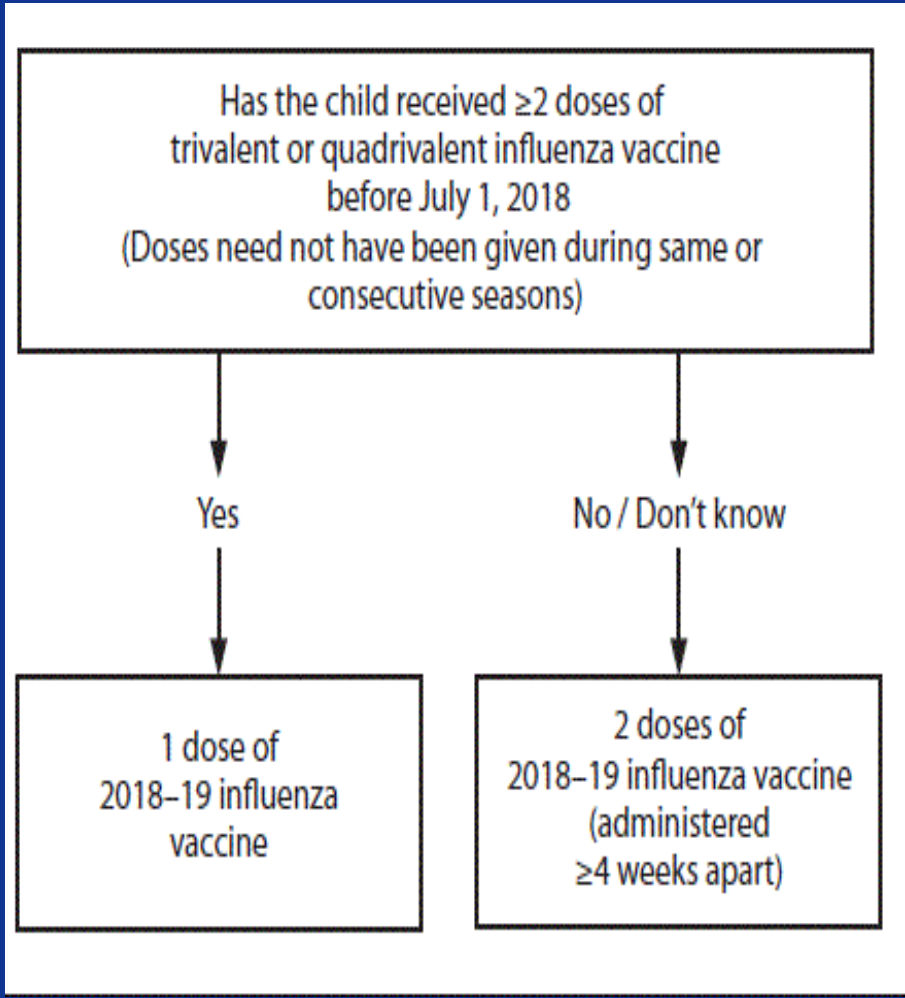
1. 0.5 mL FluLaval Quadrivalent®
   - 15 μg of HA per vaccine virus
2. 0.5 mL Fluarix Quadrivalent®
   - 15 μg of HA per vaccine virus
3. 0.25 mL Fluzone Quadrivalent®
   - 7.5 μg of HA per vaccine virus

LAIV4

- 0.2mL intranasally (0.1 mL each nostril)

Number of Doses <9 YO

- 2 dose requirement
  - ≥2 total prior doses
  - Any flu vaccine
  - >4 wks apart
  - Before 07/01/18
  - Even if 2 doses not in same or consecutive seasons
- Met 2 dose requirement
  - **Yes** - only 1 dose in 2018–19
  - **No** - 2 doses in 2018–19
    - Interval at least 4 wks



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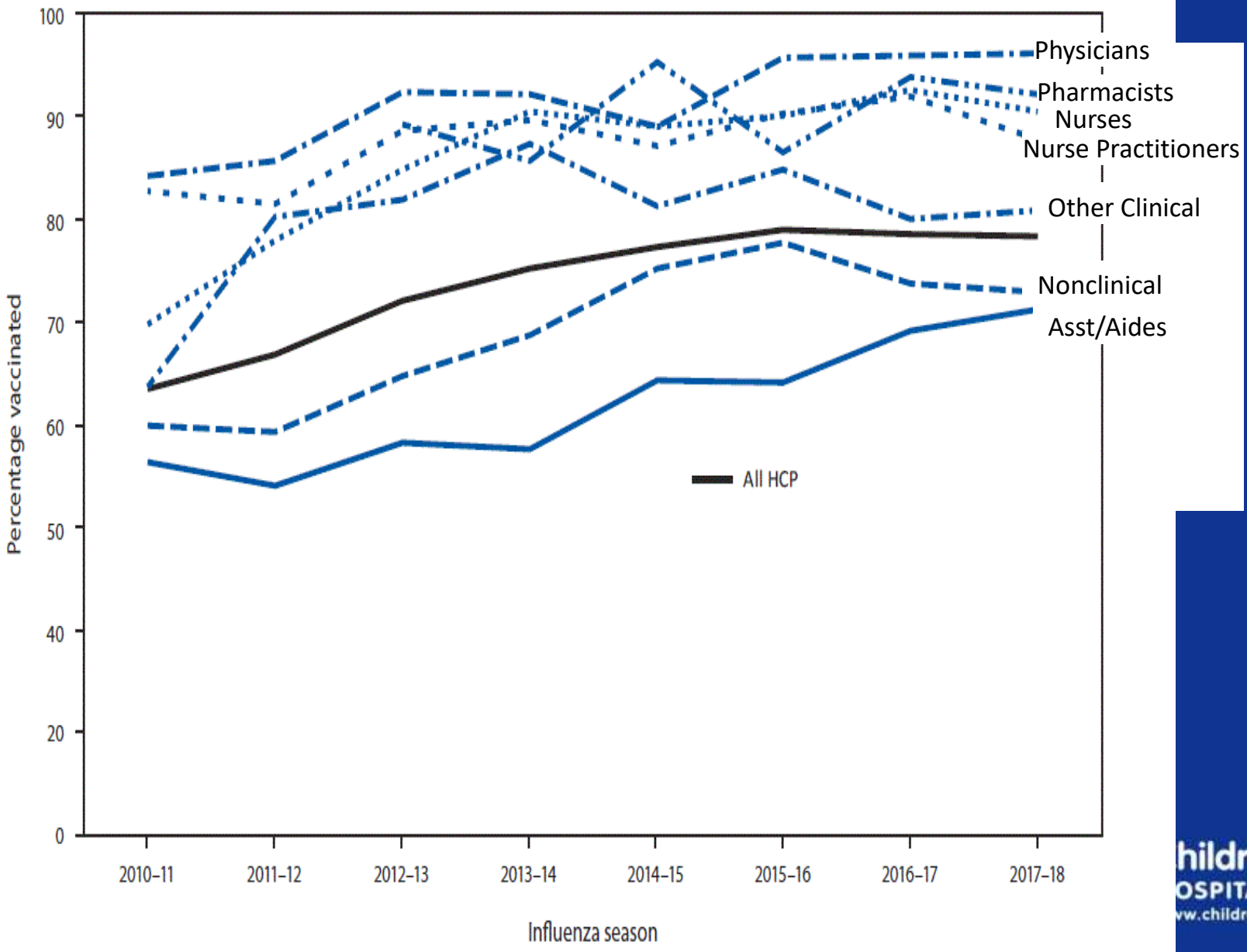
LAIV4 Option

- Low LAIV VE in US vs A/H1N1 (2013-2014 and 2015-2016)
  - LAIV not recommended in past 2 US seasons
- 2018-19 LAIV4 different than prior years
  - New seed strain
  - H1N1pdm09-like vaccine virus (A/Slovenia/2903/2015)
  - Induced higher immune response in pilot study
- VE of new LAIV not known yet

Other Influenza Recs from AAP/ACIP

- Pregnancy
  - Dose any time during pregnancy
  - Unless true contraindication
- Postpartum but no flu vaccine during pregnancy
  - Dose before hospital discharge
- Breastfeeding
  - Vaccine during safe for mothers and their infants
- Egg allergy - no added precautions above those for any other vaccine*

HCW Flu Vaccine Uptake Rising



CMH - >90% since 2012

Place of Vaccination 2017-18

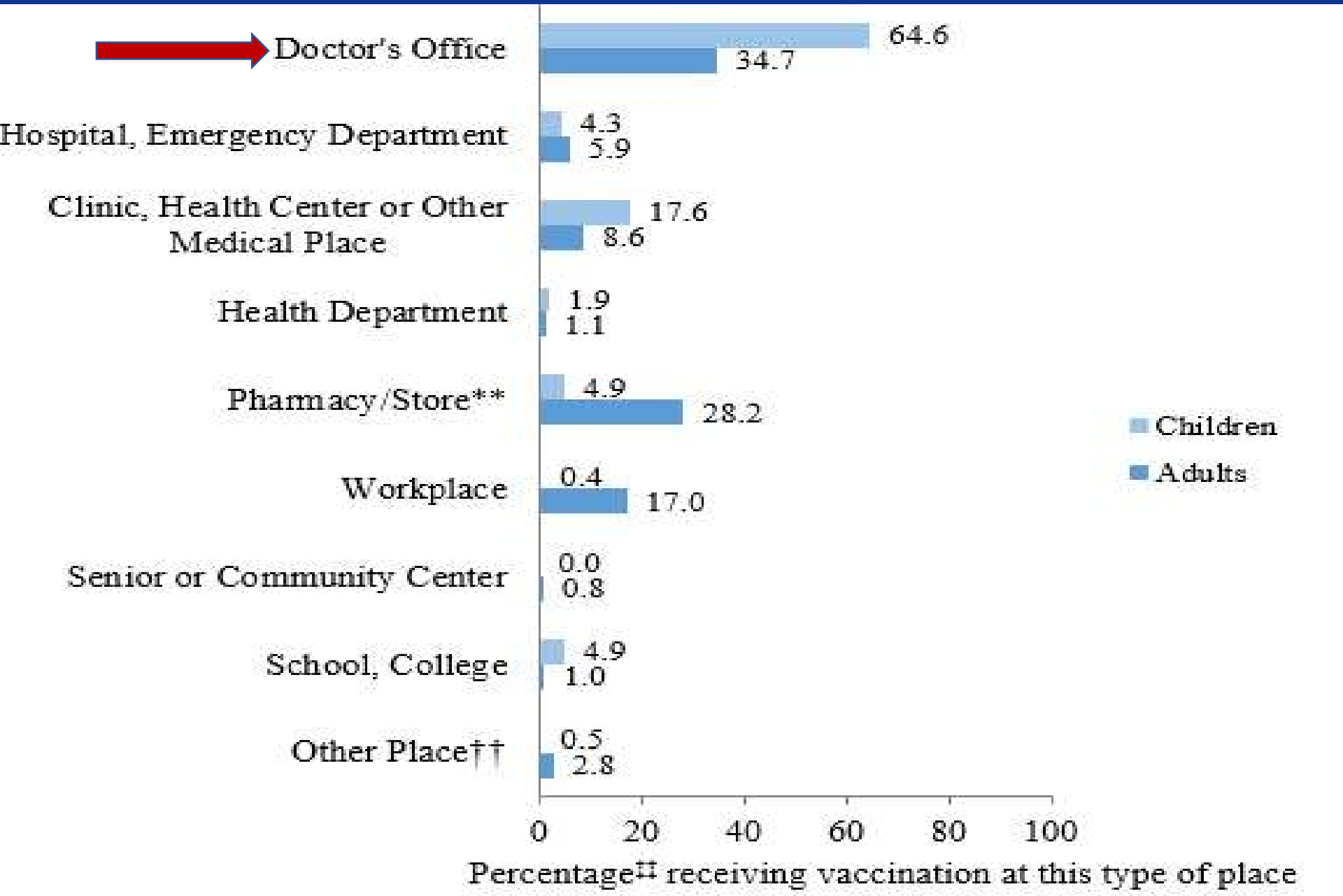
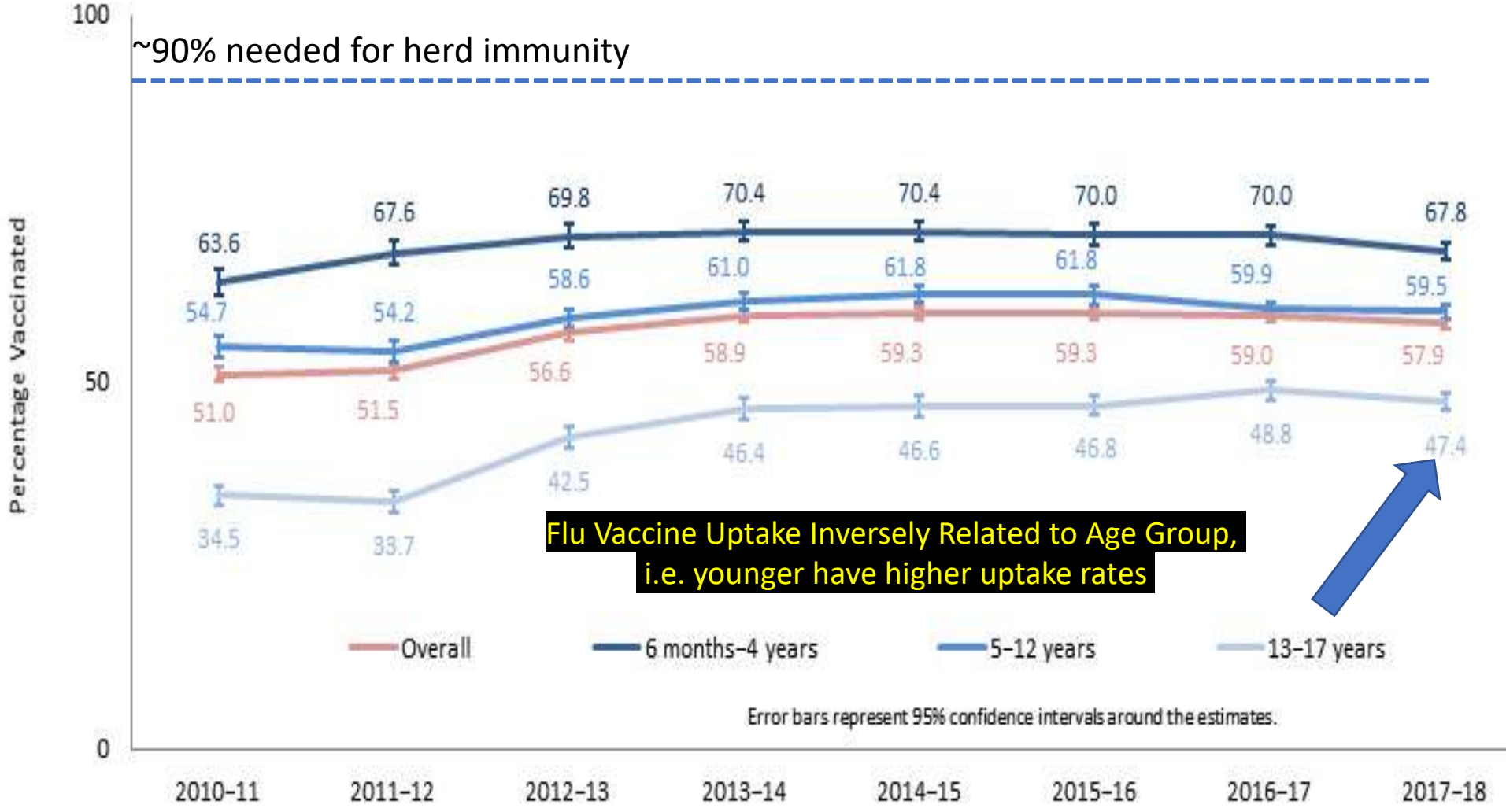


Figure 1. Flu Vaccination Coverage by Age Group and Season, Children 6 Months—17 years, United States, 2010–2018 MMWR - CDC Data



*** 7.7 percentage point decrease in coverage among Hispanics**

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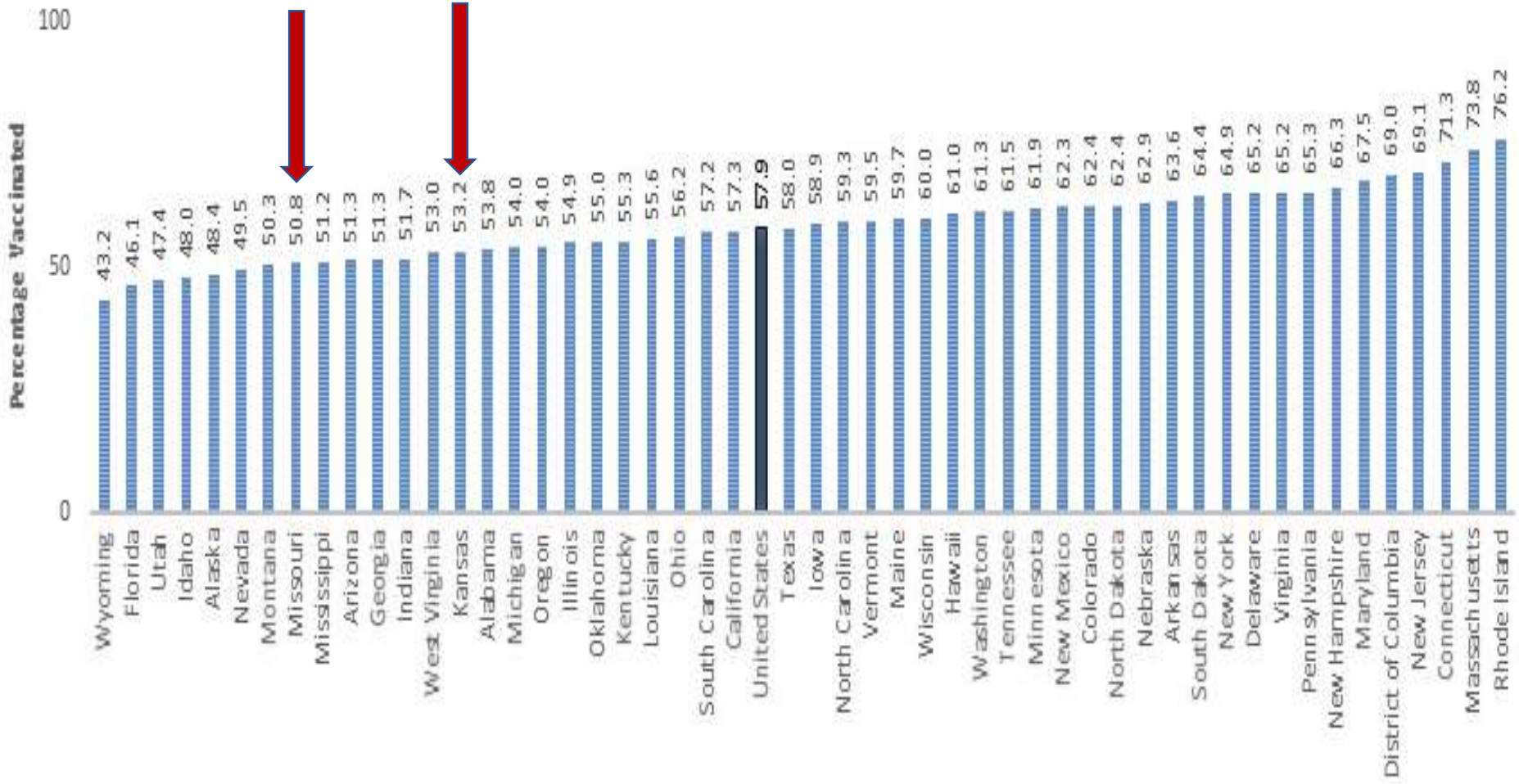
Figure 2. Flu Vaccination Coverage by State, Children 6 Months—17 Years, United States, 2017–18 Season



Waning Intra-seasonal Protection

- "Balancing considerations of unpredictability of timing of influenza season onset and concerns that vaccine-induced immunity might wane over the season, it is recommended that vaccination should be offered by end of Octo

MMWR Sept 2018

- Children needing 2 doses
  - 1st dose as soon as available
- Should we revaccinate already fully vaccinated persons later in season?
  - Not recommended

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Waning Intra-seasonal Vaccine Protection

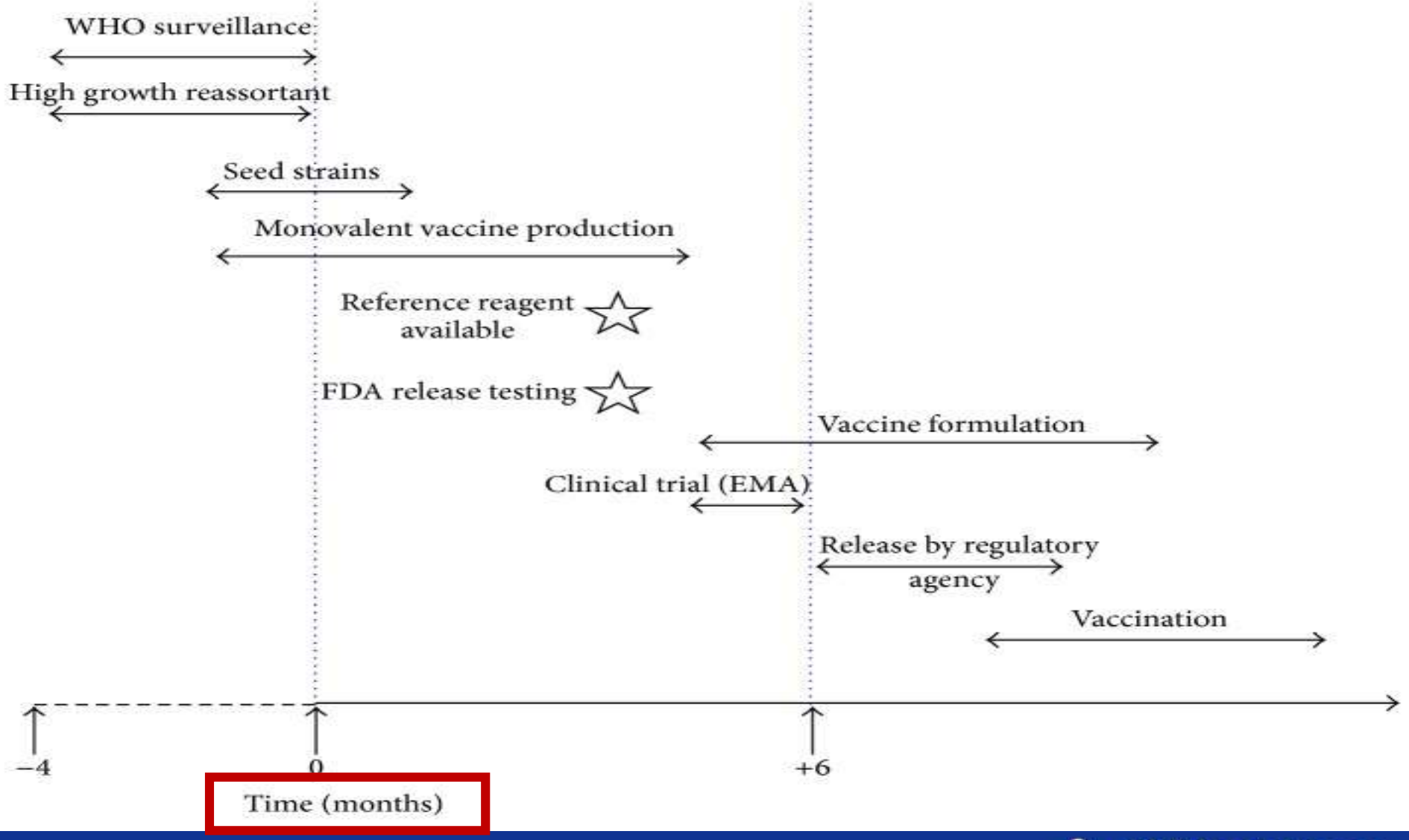
- Delaying influenza vaccine
  - Might result in greater immunity later in the season
  - Likely results in some missed vaccination opportunities
    - More constrained time period and some may not return
- 8 studies - Conflicting results
  - Waning effects not observed consistently
- “Waning varies by:
  - Age (oldest and youngest), virus subtypes, and seasons
- ? partly due to unmeasured confounding bias or late season drift-variants not well-matched to vaccine strains
- May be greater with A(H3N2) than A(H1N1) or B viruses

- Refs at end of presentation

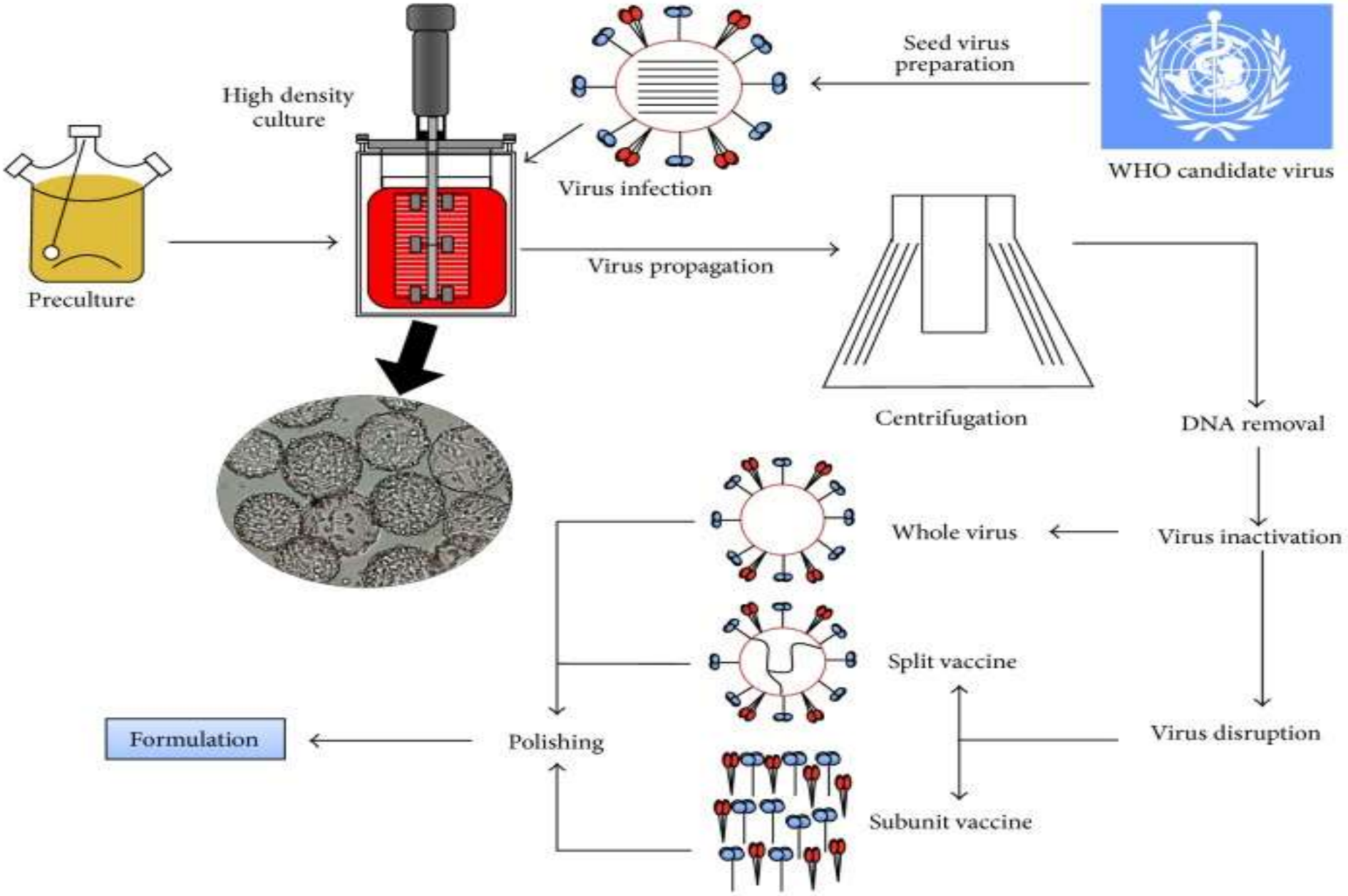
Original Immunological/antigenic Sin

- 1st infection or 1st vaccine
  - Permanently imprints immune system
  - Persistent dominant immune memory and amnestic response for that influenza strain/s regardless of strain seen in future
- When exposed to other strain/s
  - Wild type virus in nature or other vaccine strains
  - Immune system not as effective in generating protective responses to new strains

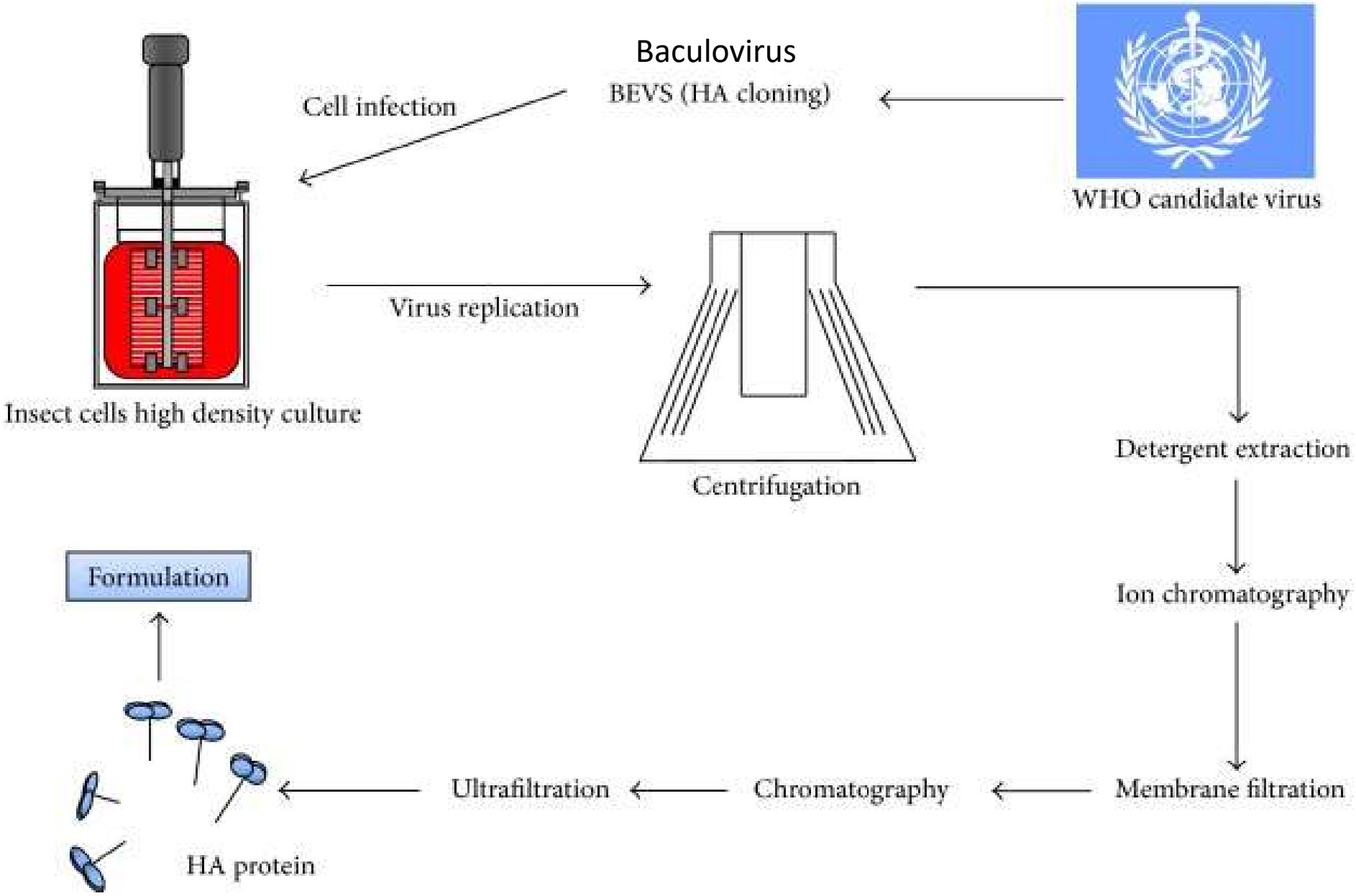
Seasonal Flu Vaccine Timeline



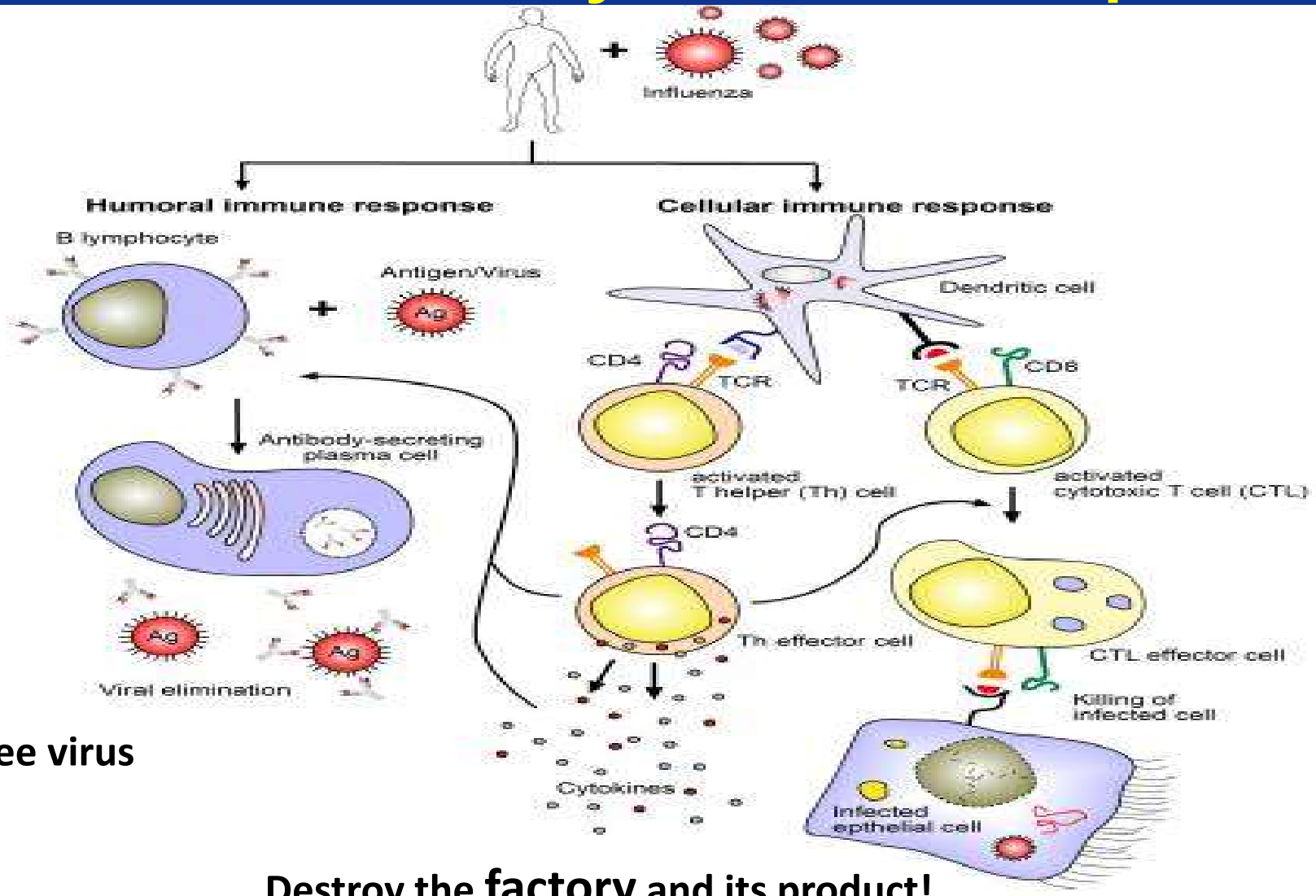
Influenza Non-egg based Vaccine Formulation



Influenza Non-egg based Vaccine Formulation - 2



Best Protection: Antibody + Cellular Response



Neutralize free virus

Destroy the factory and its product!

Cell Culture-based IIV (cIIV4) vs egg-based IIV3

- Low 2017-18 VE (~24% overall)
  - Flu antigens from eggs drifted vs those in circulating strains
  - Cell derived flu antigens do not drift
  - ? cell-based vaccines have had higher VE last year
  - Relative VE (cIIV vs egg derived IIV)
  - Absolute VE of each vaccine alone
- Kaiser Permanente-North CA, 3 million 4-64 yo
  - ~1 million vaccinated; ~8.3% vaccinees got cIIV
  - ~5,800 influenza A-positive
    - 70% unvaccinated
    - ~25% got egg-based IIV3, 2.4% got cIIV

Cell Culture-based IIV (cIIV4) vs egg-based IIV3

- Absolute VE for Flu A strains vs no vaccine
  - cIIV4 = 31.7%, 95% CI 18.7%-42.6%, *P*<0.0001)
  - egg-based IIV3 = 20.1%, 95% CI 14.5%-25.4%, *P*<0.0001)
- Relative VE cIIV vs IIV for flu A
  - Not significantly different
  - Overall (A+B strains) – P<0.01
    - cIIV4 = 40.9%
    - IIV3 = 9.7%
  - But…..
    - Most flu in CA region was B Yamagata
    - B Yamagata not in IIV3 but is in cIIV4

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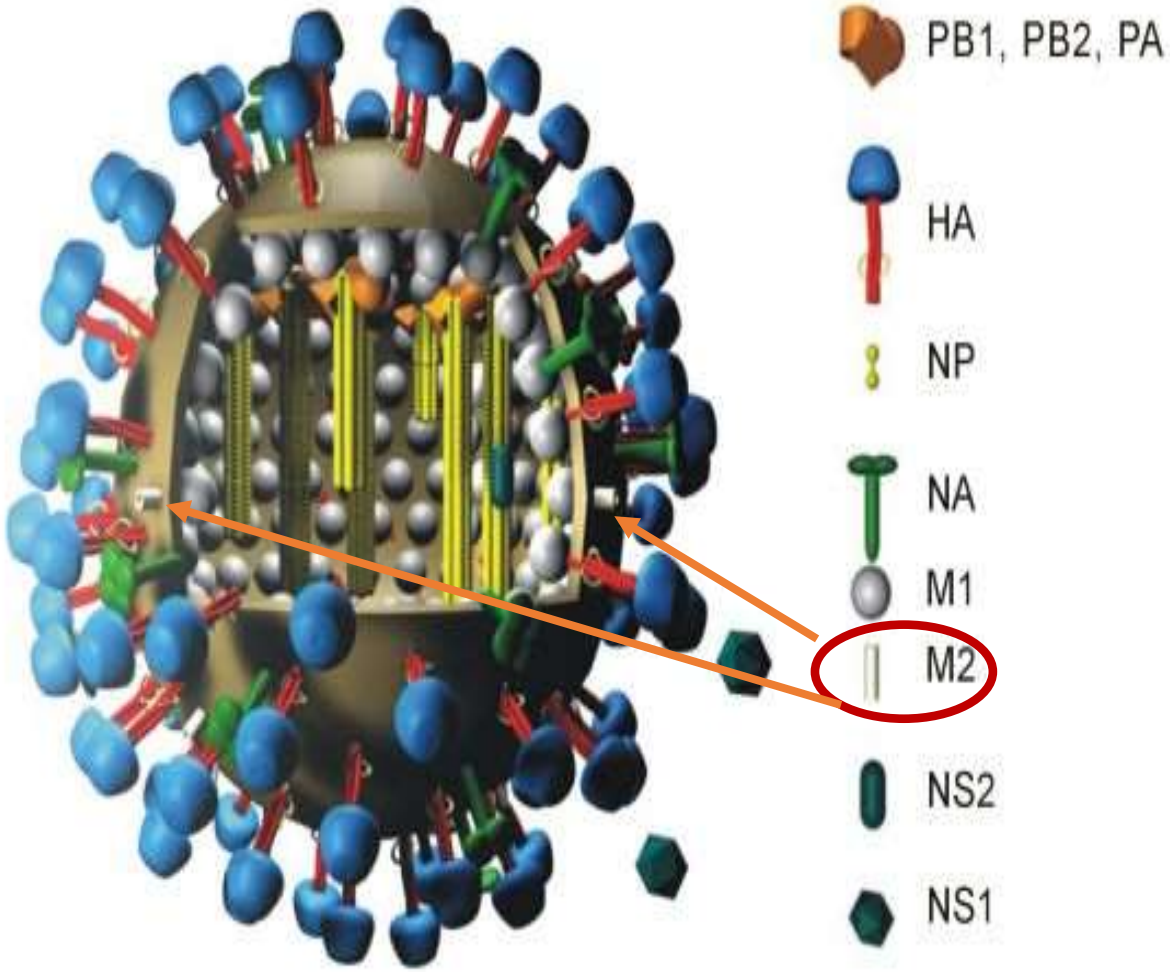
Experimental Pediatric Nasal Influenza

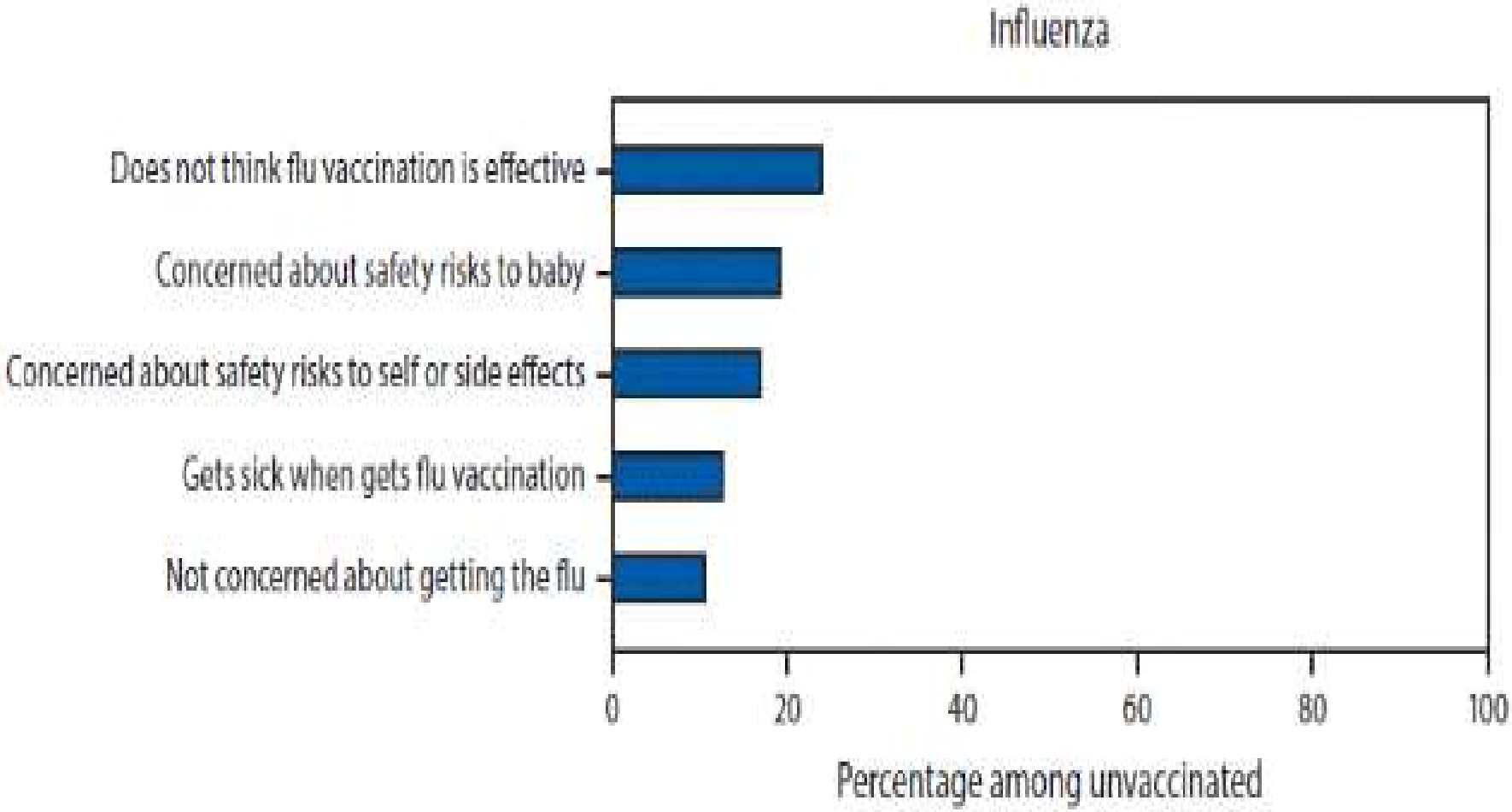
- **Goal: Protection even if vaccine mismatch for circulating strain**
- New vaccine: H3N2 genetically altered to replicate only once in vivo
- **Animal data**
  - "single replication" virus did not cause disease
  - Robust immune response similar to natural influenza infection
- **Phase 1 trial in healthy adults**
  - As safe as seasonal vaccine and robust immune responses
- **Ongoing**
  - Phase 2 adult trial currently underway
  - Phase 1 double blind placebo-controlled clinical trial in healthy 9-17yo
    - Saint Louis University's Vaccine and Treatment Evaluation Unit (VTEU)
    - N= 25 intranasal vaccine (FluGen Inc, Madison WI) and 25 placebo
    - All get licensed IIV4 3 months later
    - Metrics: Safety plus antibody and cell-mediated responses



- Single-replication live-virus that has had M2 deleted produces robust immune response with extra benefit of providing cross-reactive immune response to strains not in vaccine

M2 protein needed for ongoing replication

Why Pregnant Women Not Vaccinated (N=817)



Influenza and Tdap Vaccination Coverage Among Pregnant Women — United States, April 2018. MMWR September 28, 2018 / 67(38);1055–1059

Influenza and Tdap Vaccine in Pregnancy 2017-18 MMWR / September 28, 2018 / 67(38);1055–1059

- **49.1% reported getting influenza vaccine; 54.4% Tdap**
  - 32.8% got of both influenza and Tdap
- **Lower uptake of influenza vaccine if:**
  - Black non-Hispanics
    - 35.6% vs >50% for all other race/ethnicities
  - Less than a college degree
    - 57% vs 41%
  - Less provider visits
    - 18.1% (0 visits); 37% (1-5 visits); 50% (6-10 visits); 57% (>10 visits)
  - **No recommendation or offer**
    - 9% no rec, no offer; 38% rec but no offer; 64% rec + offer

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IIV Reduced Hospitalization Risk in Pregnancy by 40%

- From 2010-2016
  - 19,450 hospitalizations in influenzas season
- Hospitalized pregnant women (other than delivery)
  - ~50% with pneumonia or influenza discharge Dx
- Influenza A or B detected in 598/1030 (58%) who were tested for respiratory virus
- Adjusted overall vaccine effectiveness
  - Against influenza-associated hospitalization during pregnancy
  - 40% (95% CI 12%–59%)

Thomson MG, et al. *Clin Infect Dis*. 2018:doi:10.1093/cid/ciy737.

Antiviral medications

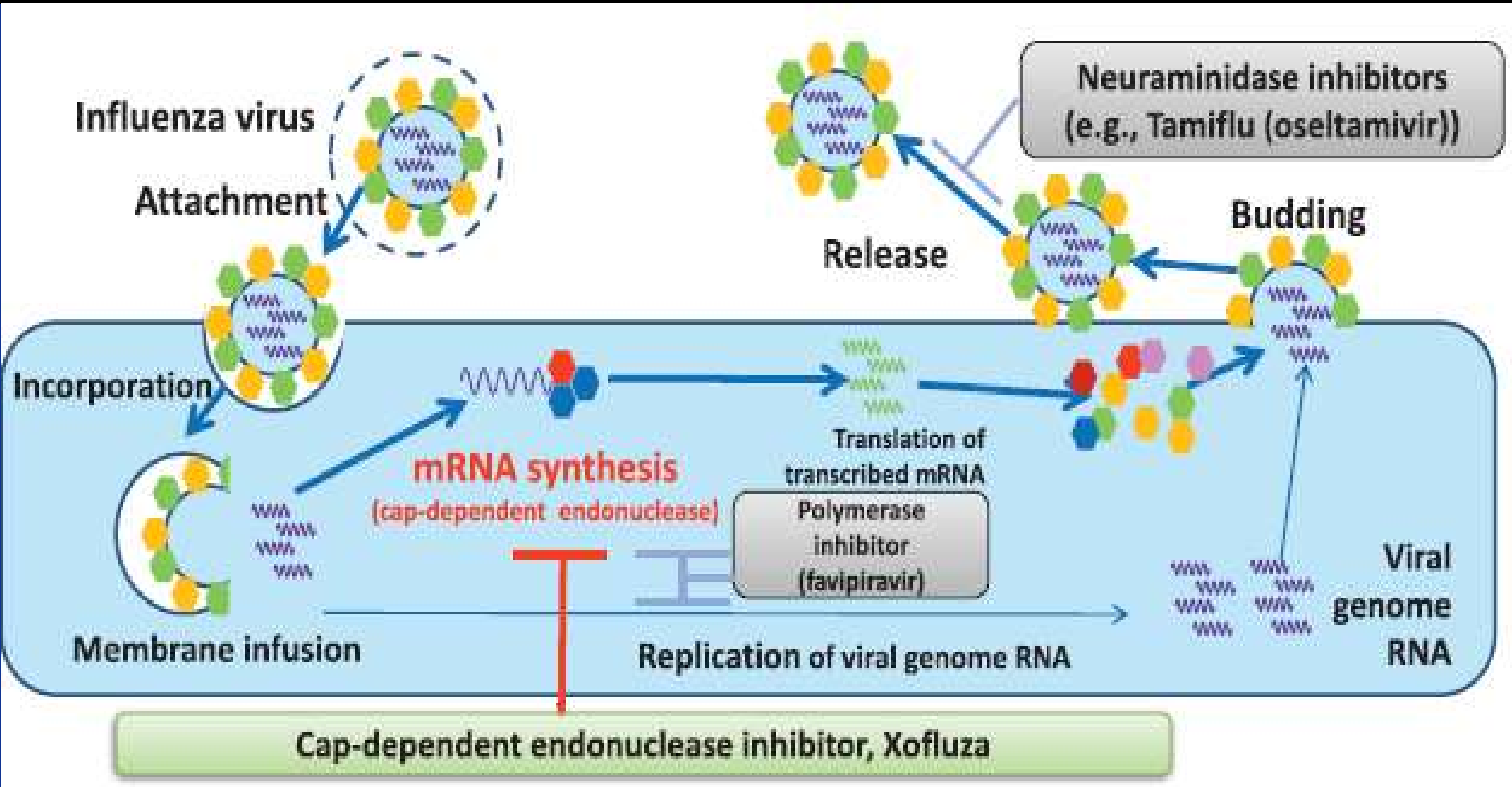
- Important in influenza Rx & control
  - But not substitute for vaccine
- Promptly identify influenza infected patients
  - Timely initiation of antiviral when indicated
  - Shared decision-making (medical + child caregiver)
- Best results if Rxed <48h post symptom onset
- BUT …. antiviral still considered >48h with
  - Hospitalization
  - Severe outpatient disease
  - Those at high risk of complications

CDC – MMWR 2018

Persons at High Risk forSevere Outcome or Complications from Influenza Infection

- Children <59 mo and adults ≥50 yo
- <18yo on ASA/salicylate-containing meds
  - Reye syndrome
- Women: are/will be pregnant during influenza season
- American Indians/Alaska Natives
- Extremely obese (BMI ≥40)
- Chronic Condition
  - Lung (asthma too), cardiovascular (not isolated HTN), renal, hepatic, neurologic, hematologic, or metabolic disorders (including DM)
- Immunocompromised - any cause
- Nursing home/long-term care facility

Baloxavir Marboxil (Xofluza®)



Oral Baloxavir marboxil for Influenza

- Novel action – endonuclease inhibitor
  - Blocks viral proliferation; inhibits start of mRNA synthesis
  - Approved in Japan Feb 2018 -under review by US FDA
- Phase III randomized US/Japan trial (N=1436)
  - 84% H3N2 influenza: single 40 or 80mg baloxavir dose
  - Otherwise healthy 12-64 yo
- Outcome - similar to 5d oseltamivir
  - Best if 1st dose within 24h post 1st Sx
  - Sx improve d2 vs d5 for placebo
  - Sx stop (54h) vs placebo (80 h)
    - Sx duration 26% shorter in adults, 39% shorter in teens
  - Shedding (1d) vs oseltamivir (3d) or placebo (4d)
- AEs same as placebo – diarrhea in 1.8% most common

1. Hayden FG, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. NEJM 2018; 379:913.

2. Baloxavir presentations at ID Week Oct 2018, San Francisco

Variant Influenza Strains - Animals?

1. **Kansas cattle with bovine respiratory disease**
   - Influenza C detected by real-time PCR testing
   - Closely related to human -C strains (≈95%)

     Zhang H, et al. Influenza C in Cattle with Respiratory Disease, US, 2016–2018. EID 2018;24(10):1926-1929.

2. Migratory Birds w Eurasian-origin influenza in US
   - Wild birds in western Alaska
     - H1N2, H3N2, H3N2/N6 (mixed infection), H3N8, H4N6, H5N2, H6N2, H7N3, H8N4, and H12N2
   - Unusual A viruses to North America by migratory birds
   - Intercontinental dispersal not be as rare as once thought

Ramey AM, et al. Introduction of Eurasian-Origin Influenza A(H8N4) Virus into North America by Migratory Birds. EID 2018 24:1950-1953.

17-year Molecular Epidemiologic Survey (Hong Kong)

- East Asia important contributor
- to influenza surveillance
  - but often mismatch of vaccine and circulating strains
- Most influenza A(H3N2) and B vaccine strains circulated in East Asia >1 year before being in US or Asian vaccines
- Yearly strain drift common
  - H3N2 = 41.2%; B = 35.3%

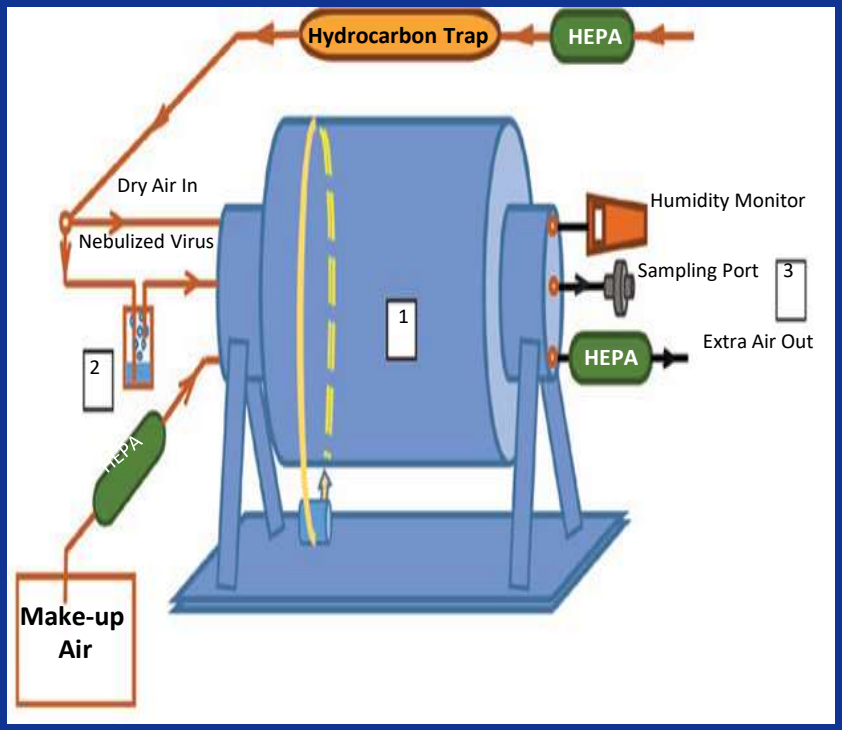
Chan M, et al. EID 2018;24(10):1825-1834.

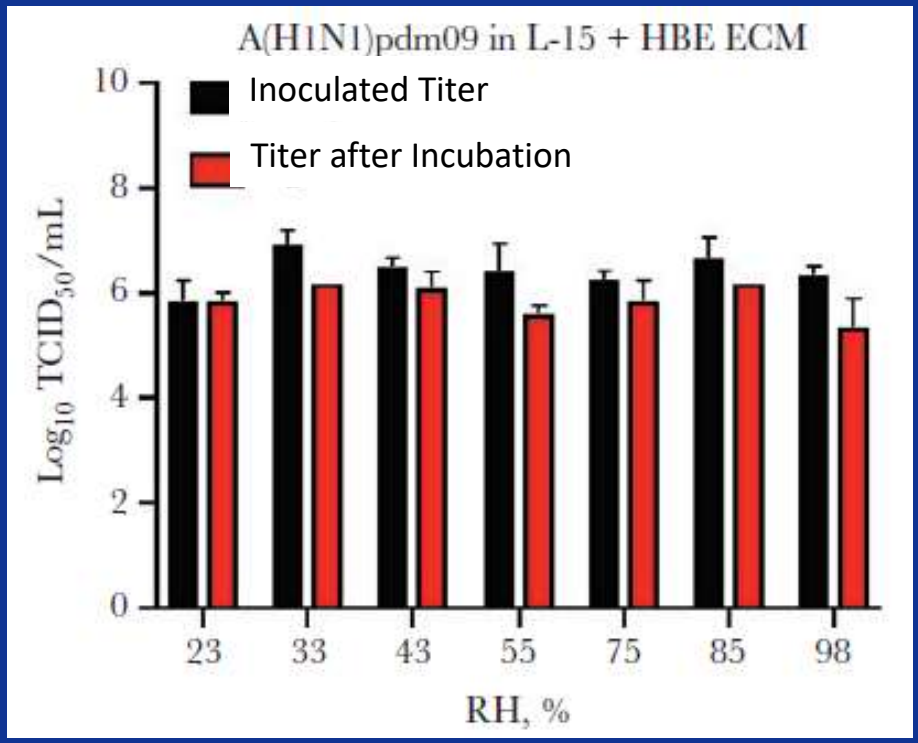
Flu on a Plane
– Sept 2018 Dubai Flight

- Commercial jets built since 1990
  - Recirculate 10%–50% of cabin air mixed with outside air
  - Filtered 20–30 times/h (HEPA filters)
  - Remove 99.9% of particles > 0.1–0.3 microns in diameter
    - Bacteria, fungi, and larger viruses or virus clumps
    - Cabin air environment not highly conducive to transmission
    - Influenza ~0.2 microns
- Highest risk on planes same as when not on planes
  - Contact with infected secretions
  - Ill person sneezes/coughs droplets that land on nose or eyes
  - Touching contaminated surface - then touching nose/eyes

https://wwwnc.cdc.gov/travel/yellowbook/2018/conveyance-transportation-issues/air-travel

Influenza Stable in Mucous at All Humidities





1. Rotating drum (1) set at desired RH
2. Bulk virus nebulized into drum (2)
3. Virus incubated: 1h w water + **lung cell proteins**
4. Samples extracted via port (3) onto gelatin filter over 15min
5. Filter dissolved to free virus for culture

Kormuth KA, et al. 2018 JID 218(5):739-747.

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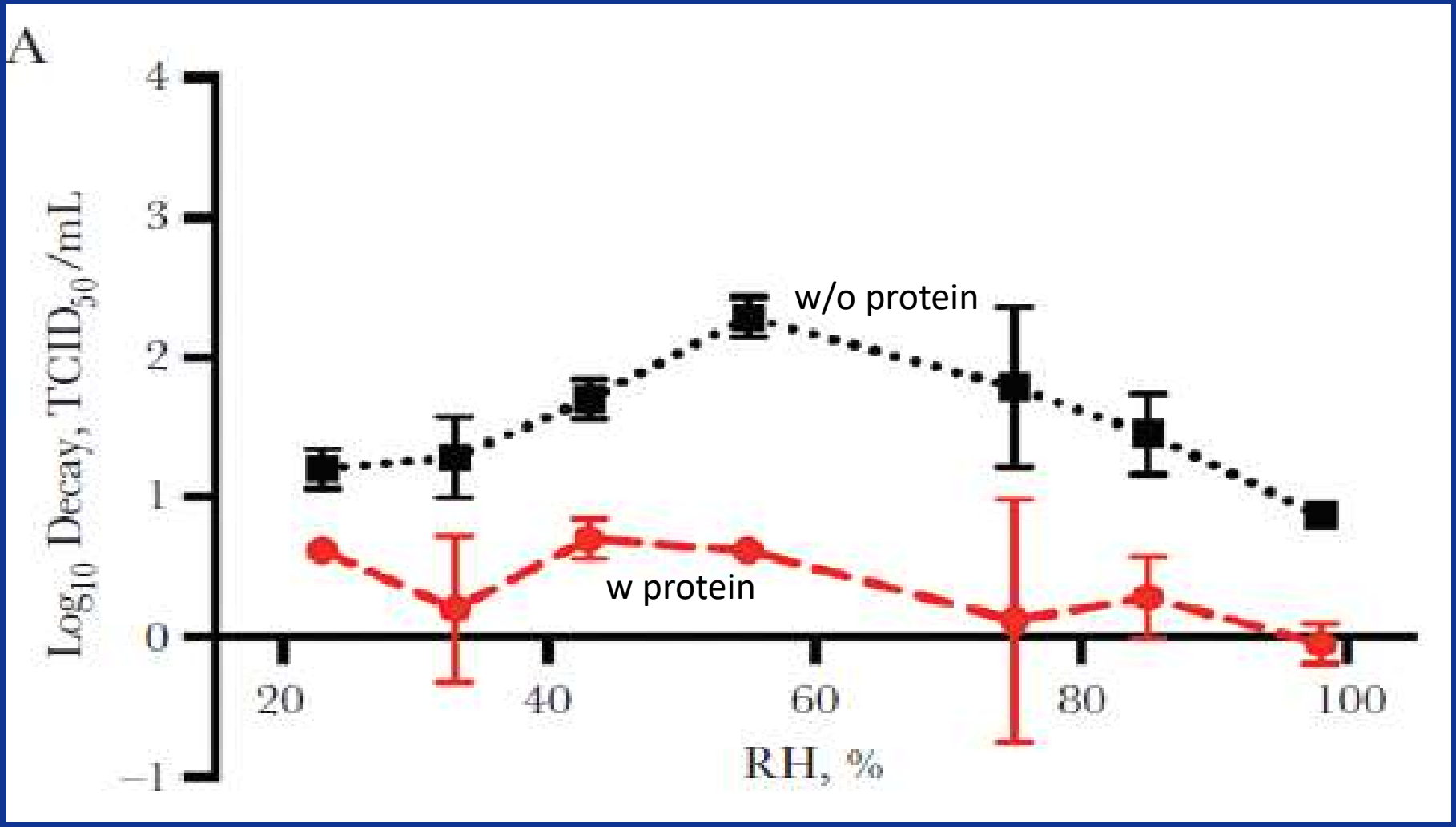
Influenza Titer Loss w/o Lung Cell Protein



Kormuth KA, et al. 2018 JID 218(5):739-747.

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Recs with History of Egg Allergy

Unlikely to be allergic If no Rxn when eat lightly cooked egg
(e.g., scrambled egg)

Still might be egg-allergic if tolerates egg in baked products
(e.g., bread or cake)

How to confirm egg allergy if desired:

1. PMH
   - Consistent adverse Rxn to eggs/egg-containing foods
2. IgE to egg proteins
   -Skin and/or IgE blood test positive

Contraindication:

- Prior severe allergic Rxn to influenza vaccine, regardless of putative responsible component

Recs with Egg Allergy Hx - 2

Any licensed, recommended, age-appropriate vaccine

1. If only urticaria (hives) with eggs
2. Also if non-hive Sx, e.g. angioedema, resp distress, lightheadedness, or recurrent emesis
3. Also even if epi or other emergency intervention used for Rxn
   - **But……for 3.**
     - Vaccine in medical setting (inpt or outpt) supervised by health care provider able to recognize/manage severe Rxn

- As with any vaccine, consider observing (seated or supine) for 15 min post-vaccine to lower syncope risk

Plan

- How was last flu season?
  - Nationally and locally
  - Pediatric risk groups
- What makes flu dangerous
- Vaccines for this year
  - LAIV use
- Last year's uptake and places dispensing vaccine
- Waning intra-seasonal protection?
- Kinds of flu vaccine – mostly now and 1 for future
- Pregnancy and flu
- Antivirals
- Effect of humidity on contagion

Ref: Waning Intra-seasonal Protection

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3. Ferdinands JM, Fry AM, Reynolds S, et al. Intraseason waning of influenza vaccine protection: Evidence from the US Influenza VE Network, 2011–12 through 2014–15. Clin Infect Dis 2017;64:544–50.

4. Kissling E, Valenciano M, Larrauri A, et al. Low and decreasing vaccine effectiveness against influenza A(H3) in 2011/12 among vaccination target groups in Europe: results from the I-MOVE multicentre case-control study. Euro Surveill 2013;18:20390.

5. Pebody R, Andrews N, McMenamin J, et al. Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: evidence of waning intra-seasonal protection. Euro Surveill 2013;18:20389.

6. Puig-Barberà J, Mira-Iglesias A, Tortajada-Girbés M, et al. Valencia Hospital Network for the Study of Influenza and other Respiratory Viruses (VAHNSI, Spain). Waning protection of influenza vaccination during four influenza seasons, 2011/2012 to 2014/2015. Vaccine 2017;35:5799–807.

7. Radin JM, Hawksworth AW, Myers CA, Ricketts MN, Hansen EA, Brice GT. Influenza vaccine effectiveness: maintained protection throughout the duration of influenza seasons 2010–2011 through 2013–2014. Vaccine 2016;34:3907–12.

8. Kissling E, Nunes B, Robertson C, et al. I-MOVE case–control study team. I-MOVE multicentre case-control study 2010/11 to 2014/15: is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination? Euro Surveill 2016;21.