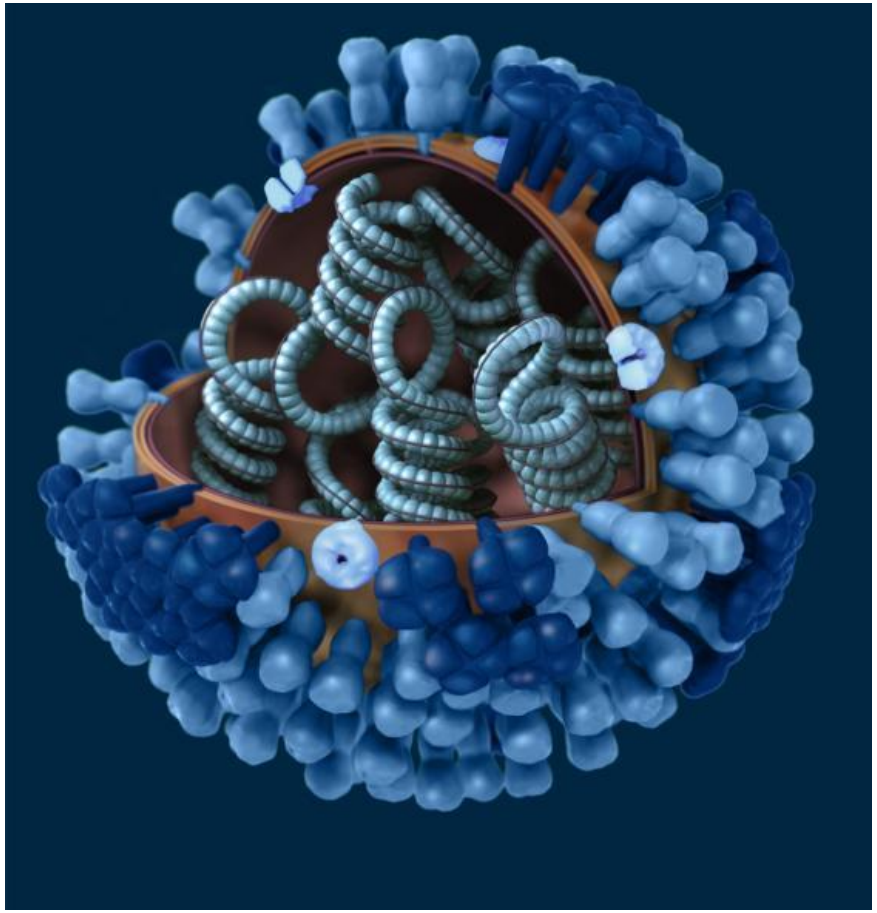
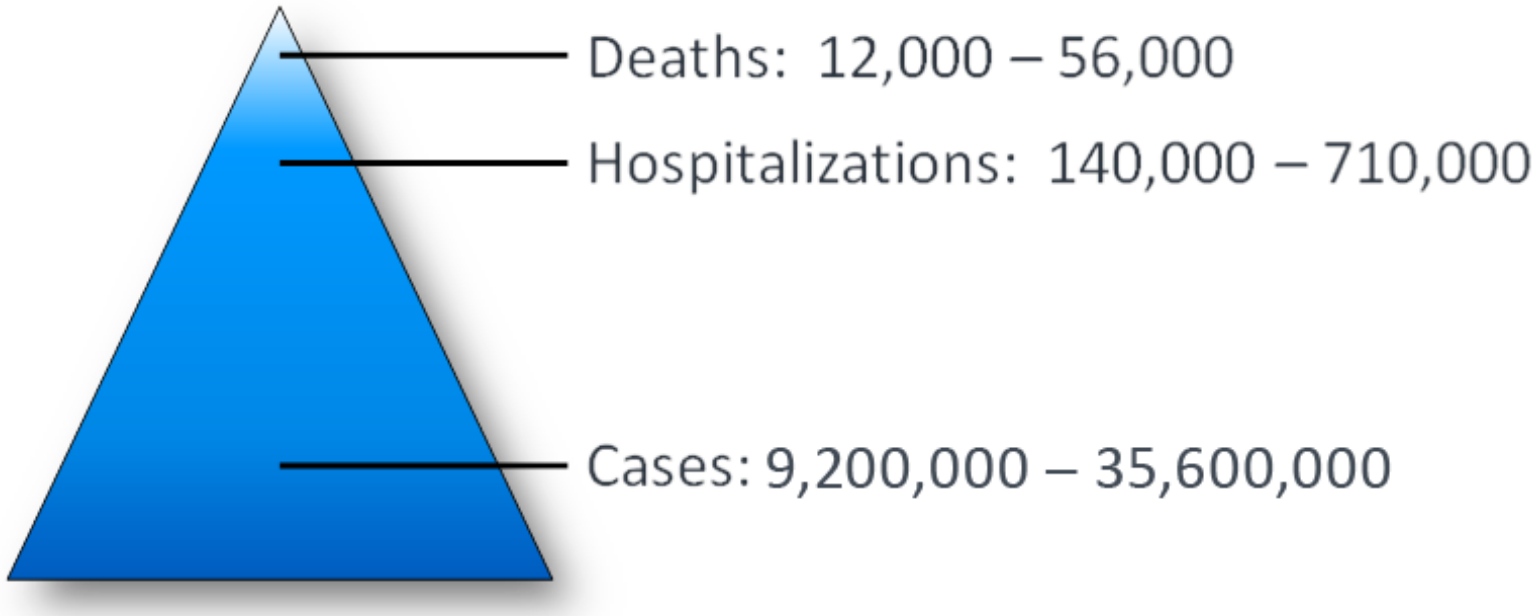
PUBLIC HEALTH
UNIVERSITY OF MICHIGAN

Influenza Vaccine Effectiveness: Local Data with Global Impact

Emily Toth Martin, MPH PhD
Assistant Professor, Epidemiology

Influenza




Deaths: 12,000 – 56,000
Hospitalizations: 140,000 – 710,000
Cases: 9,200,000 – 35,600,000

the **benefits** of **flu vaccination** 2015-2016

The estimated number of flu **illnesses prevented** by flu vaccination during the 2015-2016 season:

5 million

as many people use Denver International Airport in one month

The estimated number of flu **medical visits prevented** by vaccination during the 2015-2016 season:

2.5 million

equal to the population of Portland, Oregon

The estimated number of flu **hospitalizations prevented** by vaccination during the 2015-2016 season:

71,000

enough to fill every registered hospital bed in the state of Texas

DATA: Influenza Division program impact report 2015-2016, https://www.cdc.gov/flu/about/disease/2015-16.htm.

NCIRDig-607 | 12.06.2016

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

get **vaccinated**
www.cdc.gov/flu

It’s tough to make predictions, especially about the future…

FORTUNE

Flu Season Is Here, But How Effective Is the 2018 Flu Shot?

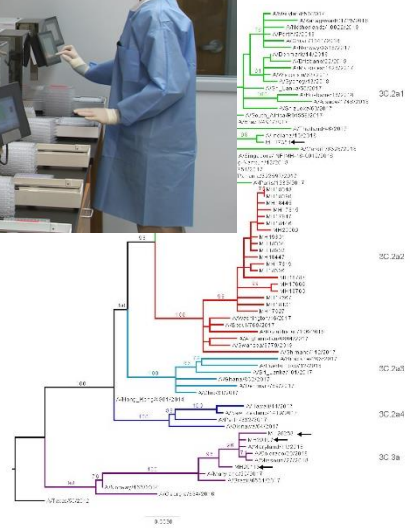
By **JACLYN GALLUCCI** Updated: September 29, 2018 3:48 PM ET

The 2018-2019 flu season has officially arrived, the Food and Drug Administration announced this week. And after last year’s flu killed 80,000 people—the highest U.S. influenza death toll in 40 years—many are questioning how effective the flu shot really is.

The short answer: No one really knows.

Yearly vaccine selection

Global Surveillance

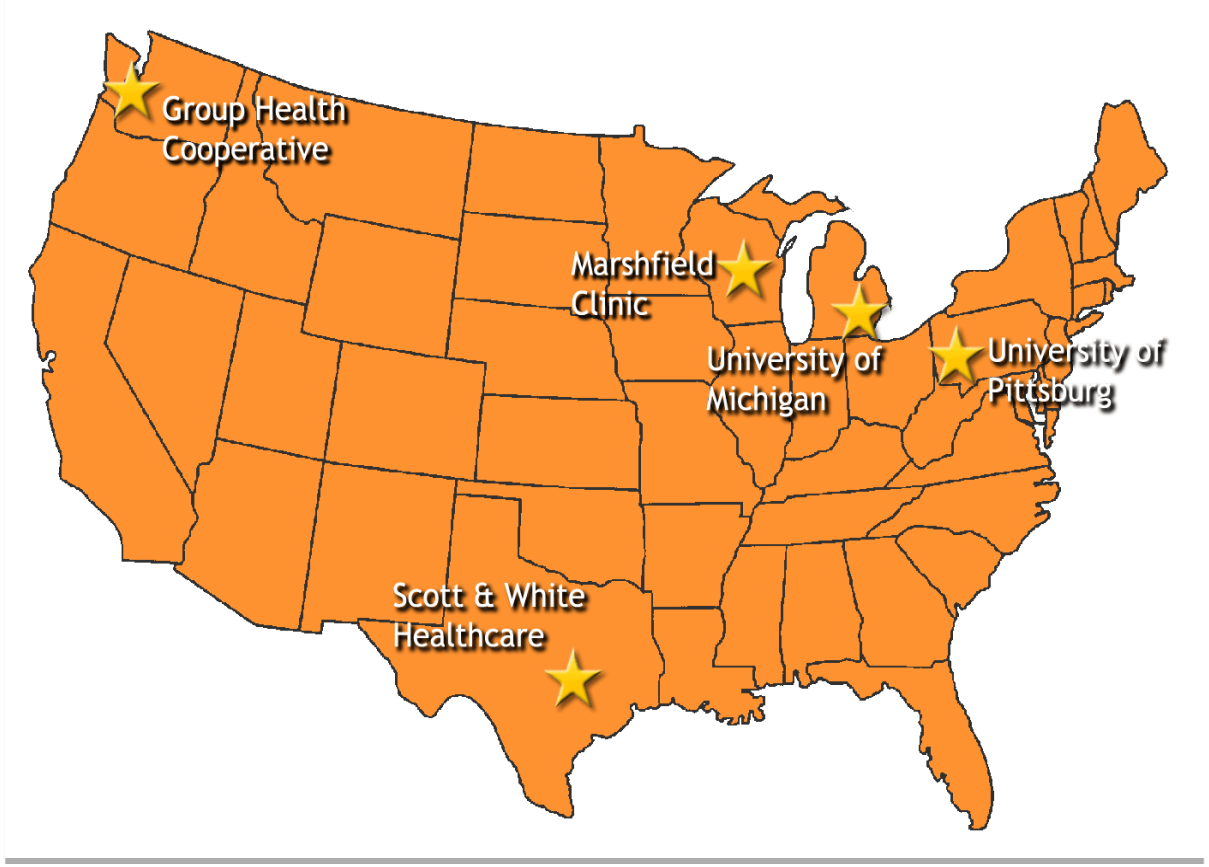


World Health Organization

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

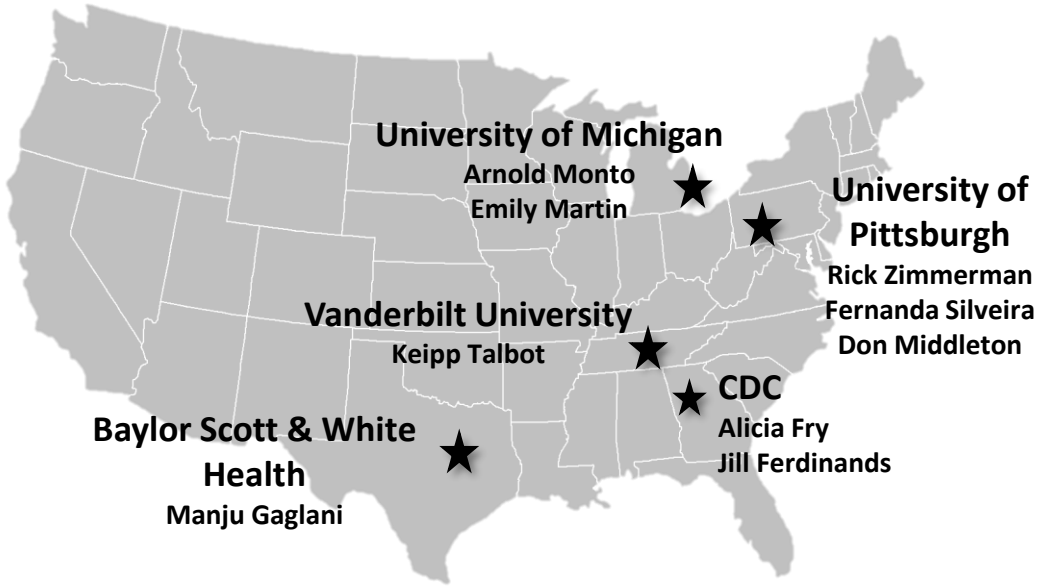
FDA

US Flu VE Network: Five Study Sites



US Hospitalized Influenza Vaccine Effectiveness Network (HAIVEN)

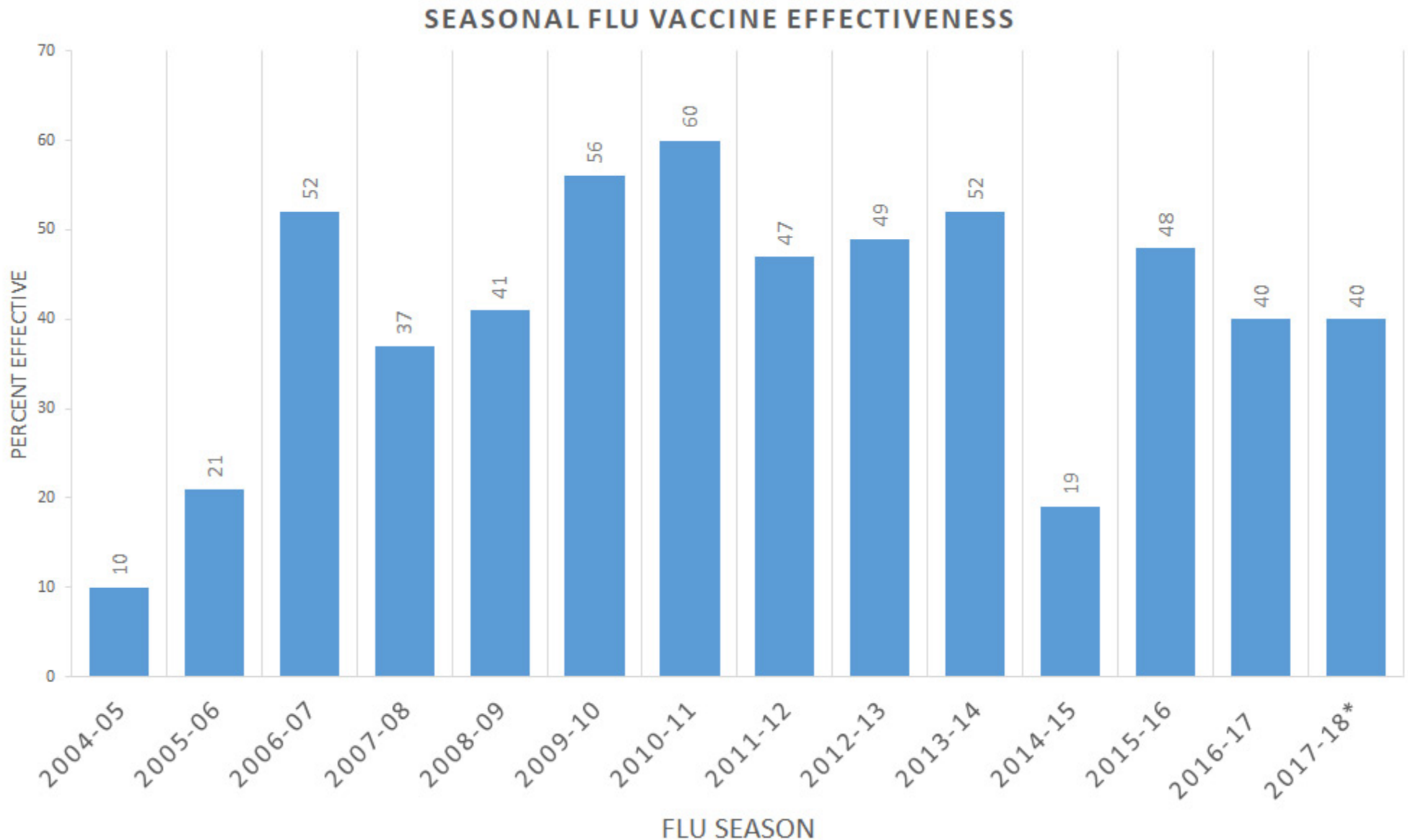
- 5 year cooperative agreement, 2015-16 through 2019-20
- CDC and 4 partner institutions
- Year 1 (2014-2015) – University of Michigan Only
- Year 2 (2015-2016) 7 hospitals with 4700 beds
- Year 3+ (2016-) now 10+ hospitals



Test-Negative Design

- ✓ Most commonly used observational design for estimating VE
- ✓ Participants are selected from people presenting with a common case definition.
  - ✓ Cough in ambulatory setting; Clinical syndrome in hospital setting
- ✓ Active surveillance in US
- ✓ Swab collected for RT-PCR testing
  - ✓ Cases: subjects testing positive for influenza
  - ✓ Controls: subjects testing negative for influenza
- ✓ Estimated ratios of the odds of influenza in vaccinated and unvaccinated subjects are used to calculate VE.

Jackson et al. Vaccine 2013; 31:2165-8.
Foppa et al. Vaccine 2013; 31:3104-9.



https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm

What we've learned…

- LAIV
- Vaccination and Severity of Illness
- Egg-Adaptations in the Influenza Vaccine

What we've learned…

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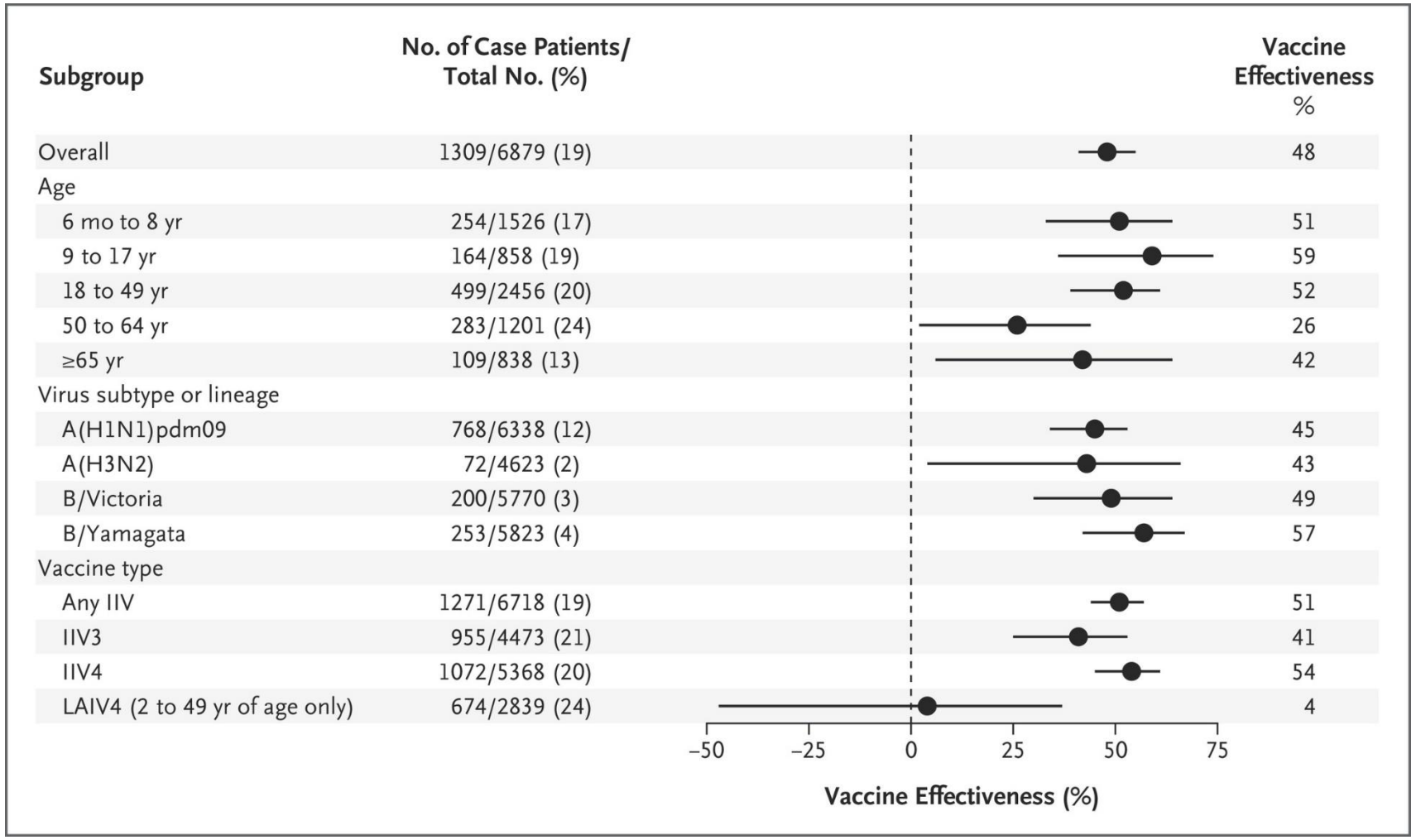
- Vaccination and Severity of Illness
- Egg-Adaptations in the Influenza Vaccine

LAIV VE Lower than IIV Overall (2015-2016)

Adjusted Estimates of Influenza Vaccine Effectiveness, Overall and Stratified According to Age, Virus Subtype or Lineage, and Vaccine Type.

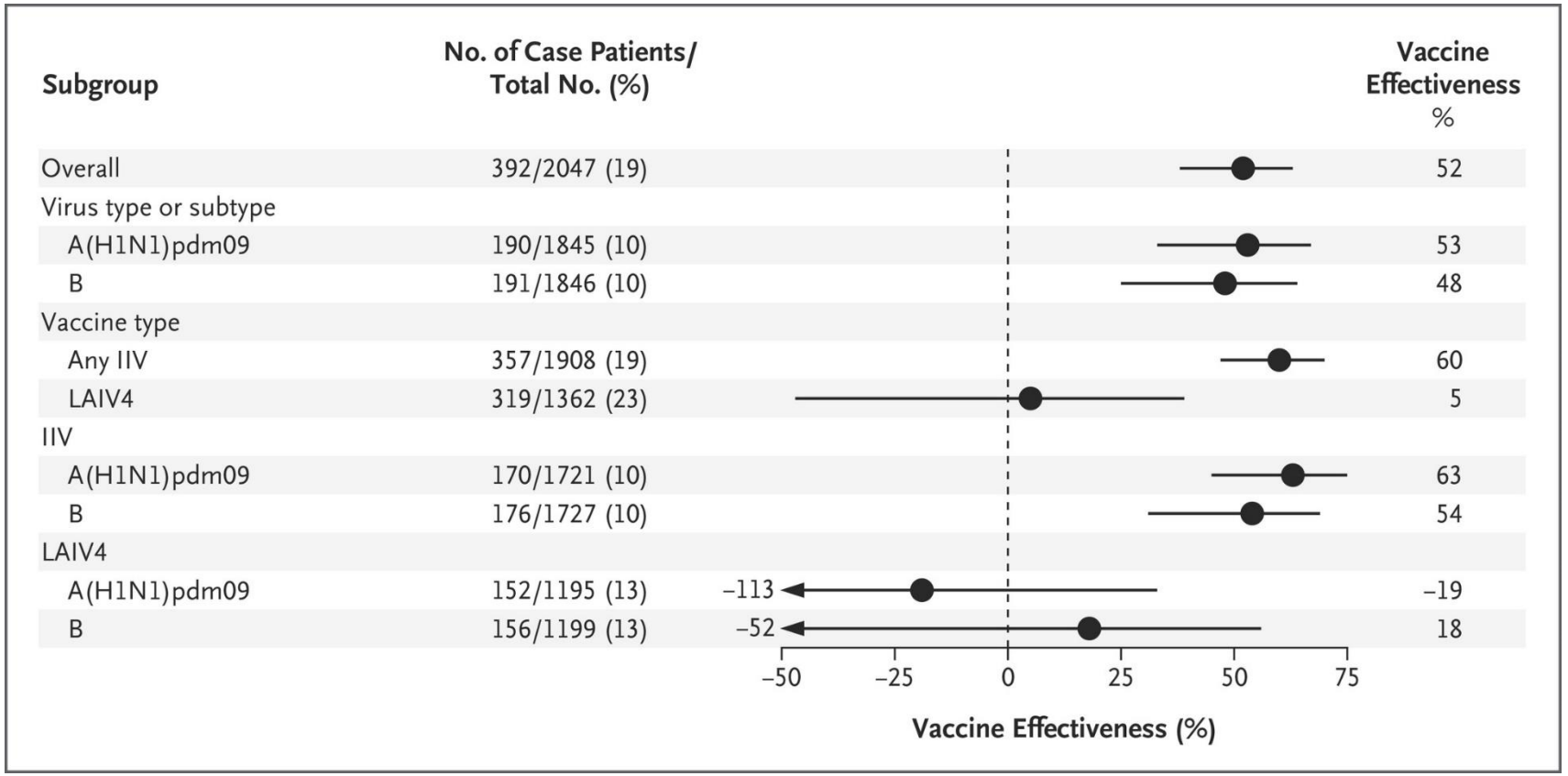


Jackson ML et al. N Engl J Med 2017;377:534-543

The NEW ENGLAND JOURNAL of MEDICINE

Results for Children 2 to 17 Years (2015-2016)

Adjusted Estimates of Influenza Vaccine Effectiveness among Children 2 to 17 Years of Age, Overall and Stratified According to Virus Subtype or Lineage and Vaccine Type.



Jackson ML et al. N Engl J Med 2017;377:534-543

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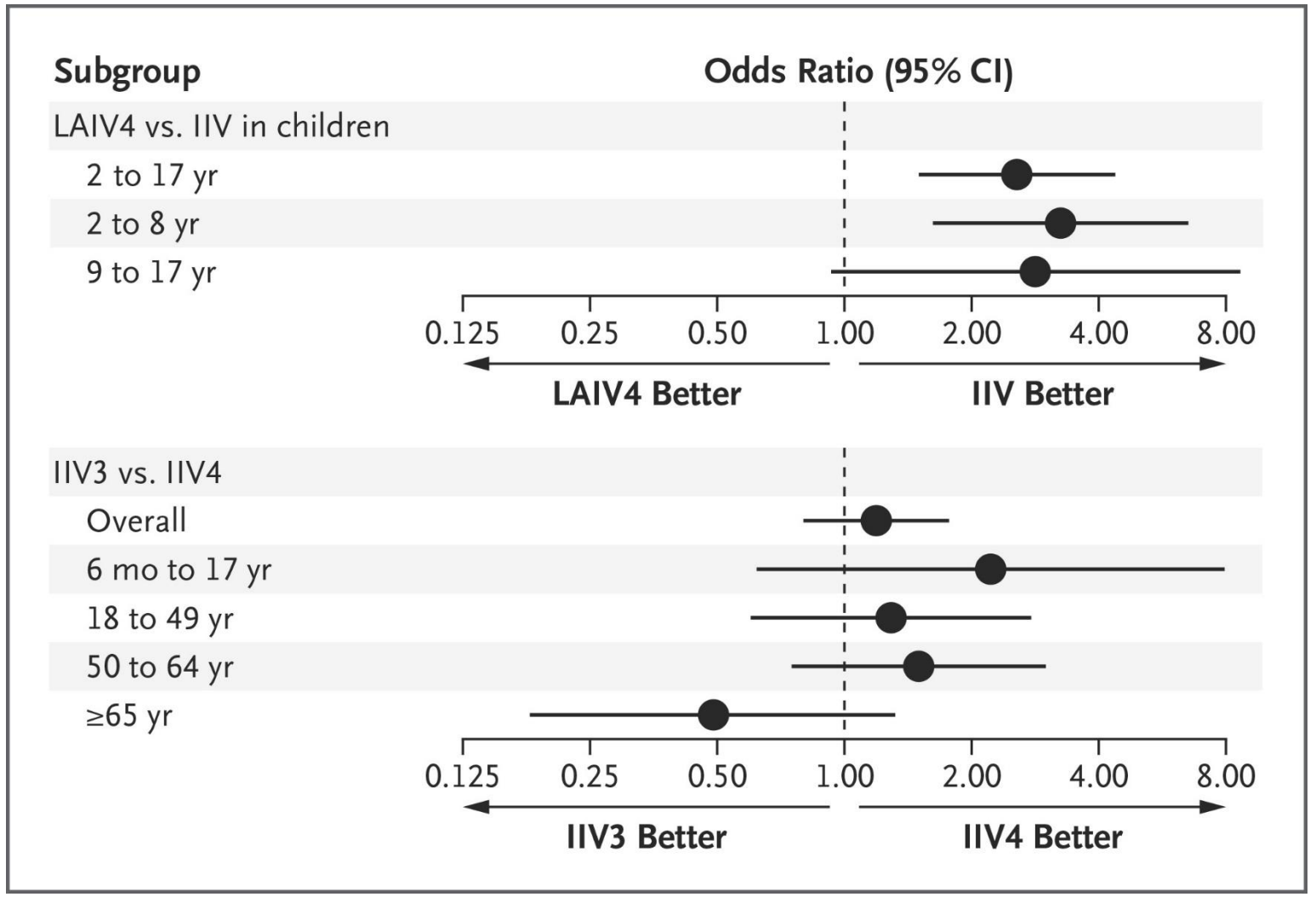
Direct Comparison of LAIV vs IIV by Age (2015-2016)

Odds Ratios for Medically Attended Influenza, Overall and According to Age Group.



Jackson ML et al. N Engl J Med 2017;377:534-543

The NEW ENGLAND JOURNAL of MEDICINE

LAIV subsequently reformulated

LETTER

Letter to the editor: Potential causes of the decreased effectiveness of the influenza A(H1N1)pdm09 strain in live attenuated influenza vaccines

CS Ambrose [1], H Bright [2], R Mallory [1]
1. MedImmune, Gaithersburg, MD, United States
2. MedImmune, Speke, United Kingdom

Correspondence: Christopher S. Ambrose (ambrosec@medimmune.com)

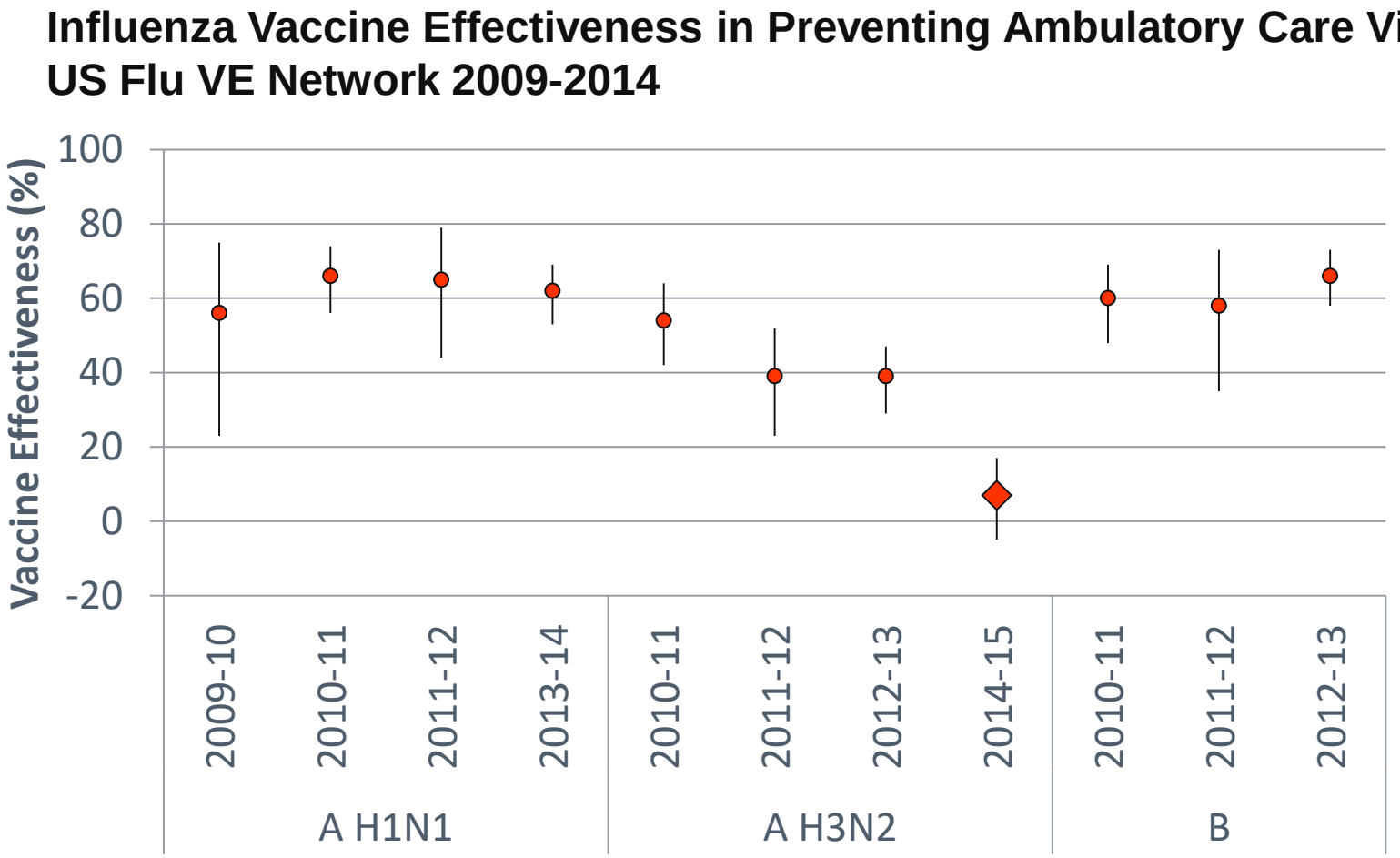
Citation style for this article:
Ambrose CS, Bright H, Mallory R. Letter to the editor: Potential causes of the decreased effectiveness of the influenza A(H1N1)pdm09 strain in live attenuated influenza vaccines. Euro Surveill. 2016;21(45):pii=30394. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.45.303942

Article submitted on 03 November 2016 / accepted on 10 November 2016 / published on 10 November 2016

What we've learned…

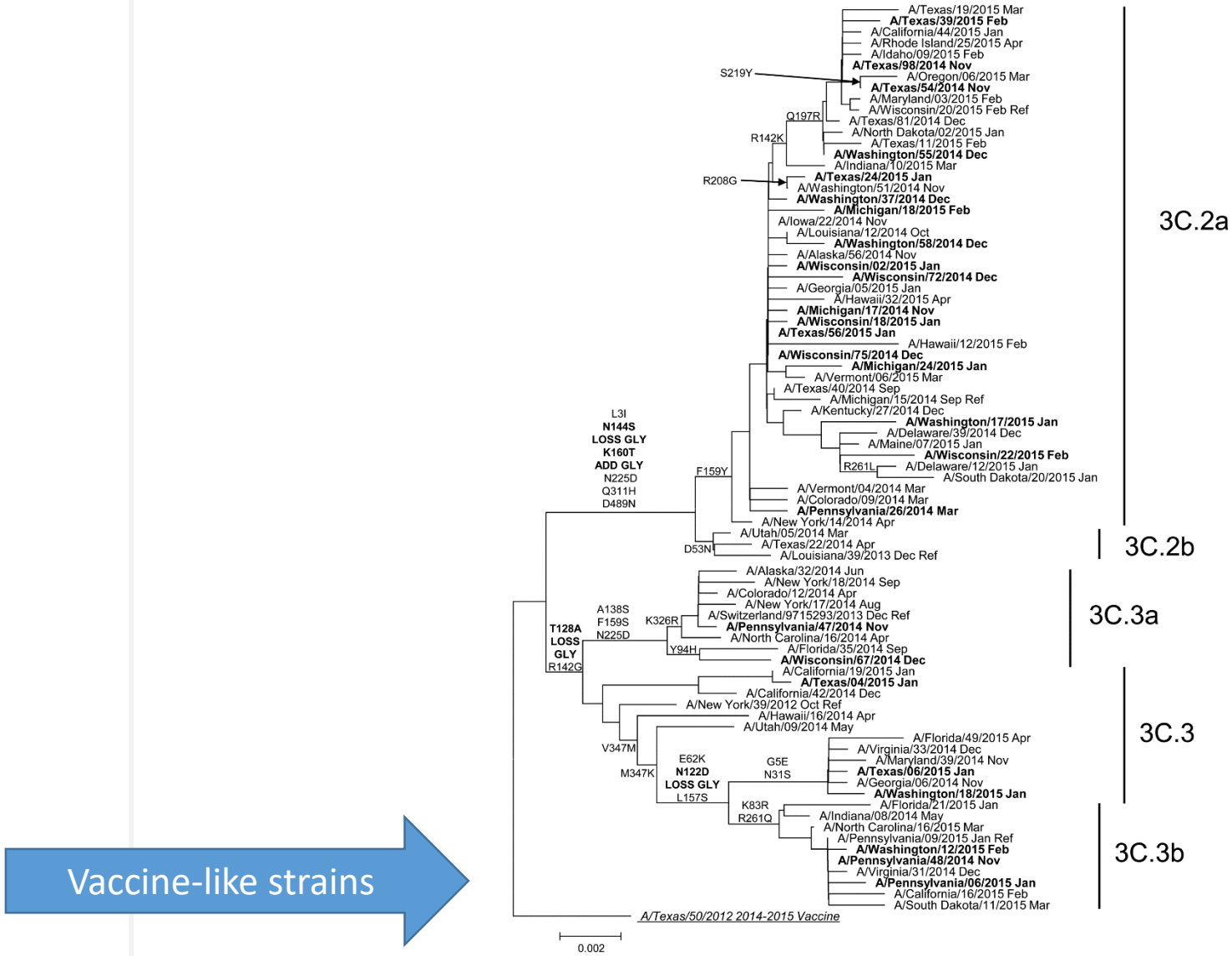
- LAIV
- Vaccination and Severity of Illness
- Egg-Adaptations in the Influenza Vaccine

2014-2015 was a bad year for the influenza vaccine



Griffin et al. *PLoS One 2011;6:e23085*
Treanor et al. *Clin Inf Dis 2012;55:951-9*
Ohmit et al. *Clin Inf Dis 2014;58:319-27*

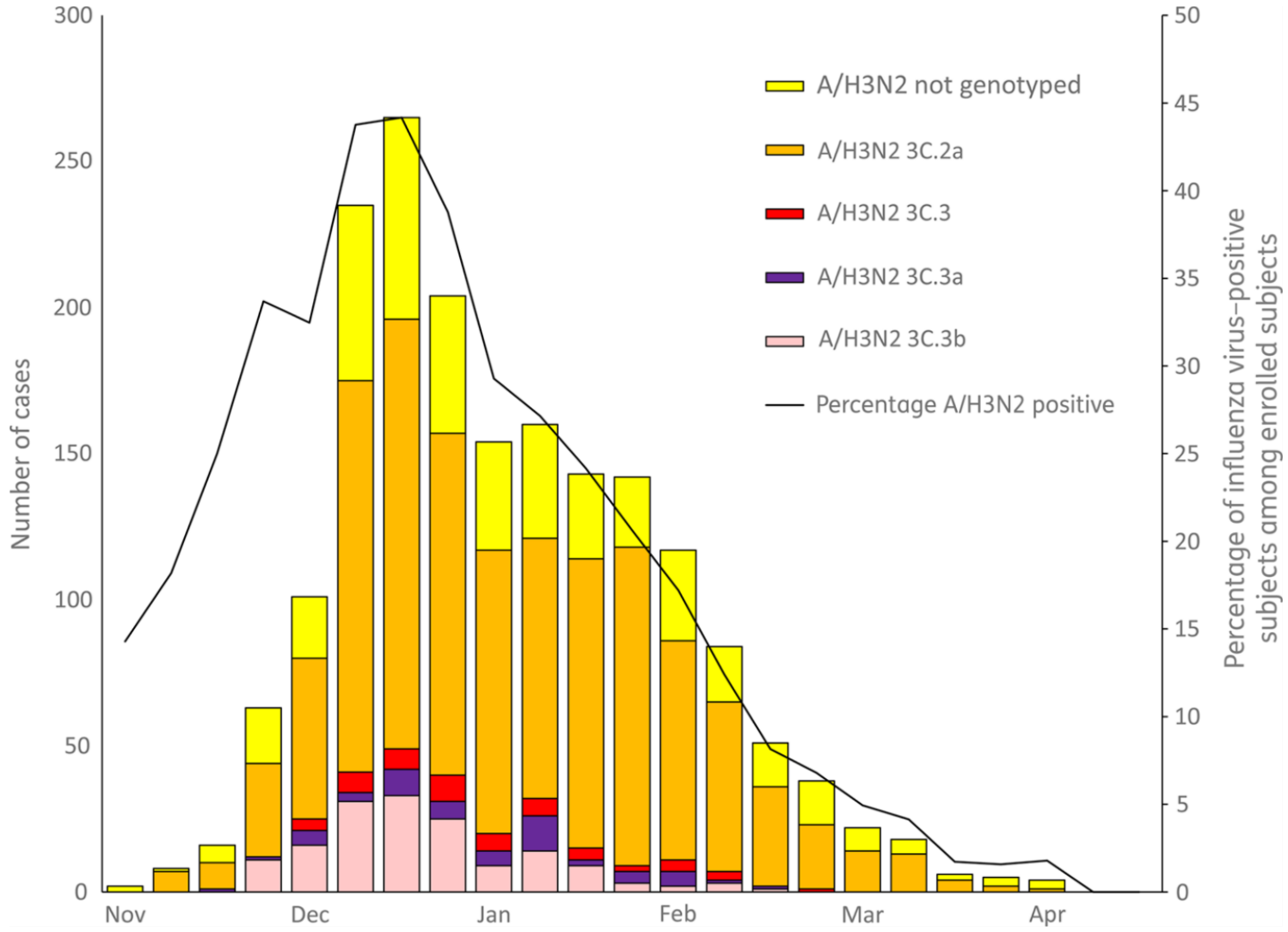
McClean et al. *J Inf Dis 2014;*
Flannery et al. *MMWR 2014;63:137-42*
Flannery et al. *MMWR 2014;64:10-5*



From: Enhanced Genetic Characterization of Influenza A(H3N2) Viruses and Vaccine Effectiveness by Genetic Group, 2014–2015

J Infect Dis. 2016;214(7):1010-1019. doi:10.1093/infdis/jiw181

J Infect Dis | Published by Oxford University Press for the Infectious Diseases Society of America 2016. This work is written by (a) US Government employee(s) and is in the public domain in the US



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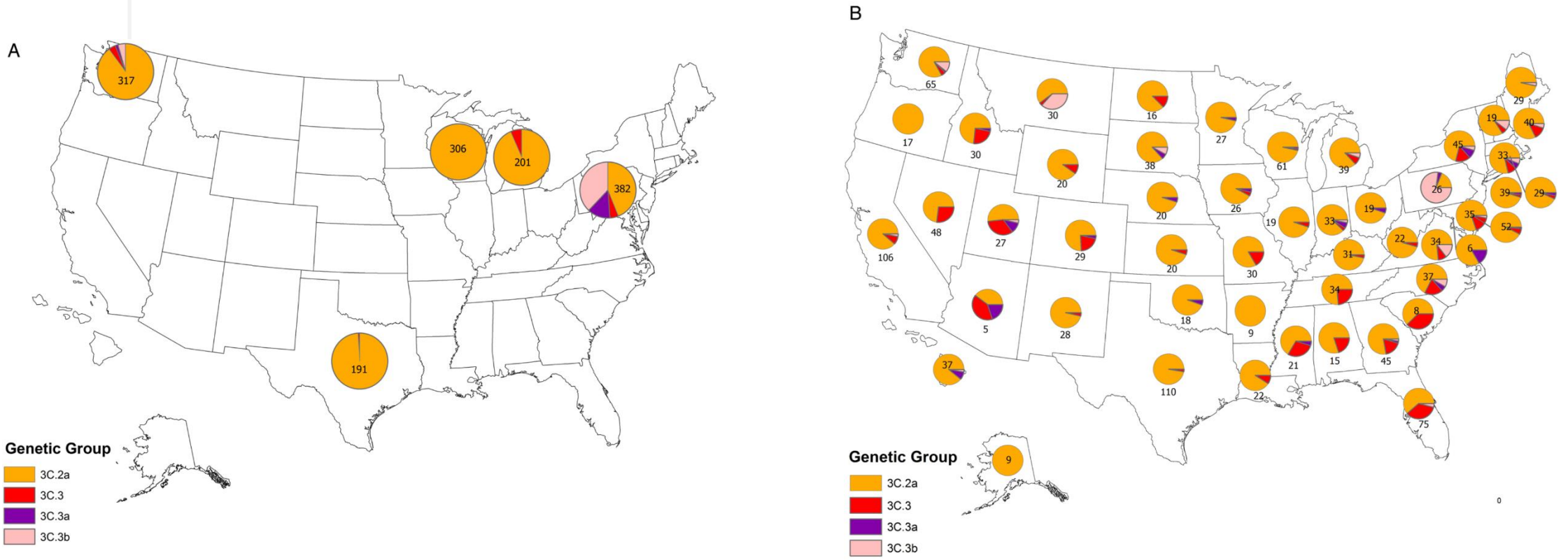

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Clinical Infectious Diseases

MAJOR ARTICLE

Influenza Vaccine Effectiveness Against Antigenically Drifted Influenza Higher Than Expected in Hospitalized Adults: 2014–2015

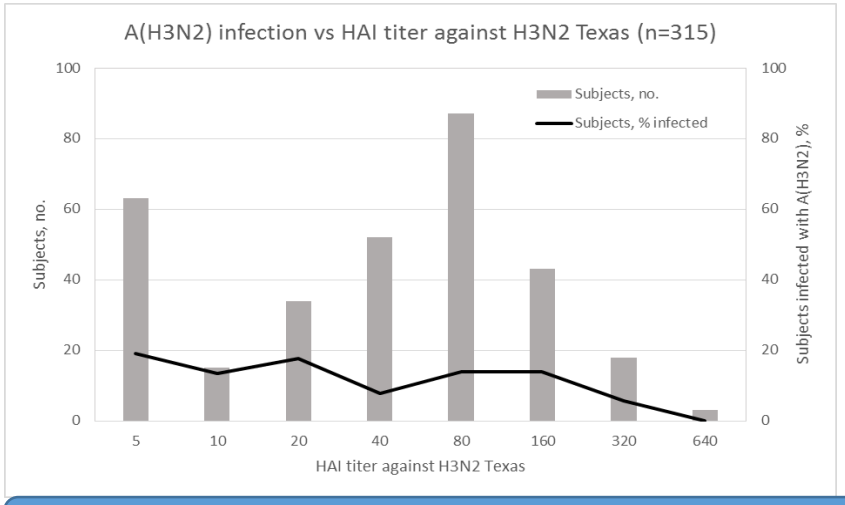
Joshua G. Petrie,[1] Suzanne E. Ohmit,[1] Caroline K. Cheng,[1] Emily T. Martin,[1] Ryan E. Malosh,[1] Adam S. Lauring,[2,3] Lois E. Lamerato,[4] Katherine C. Reyes,[5] Brendan Flannery,[6] Jill M. Ferdinands,[6] and Arnold S. Monto[1]

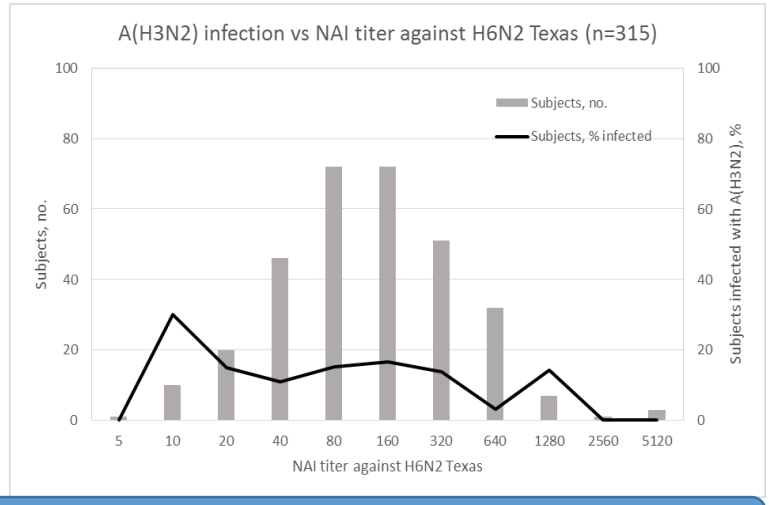
[1]Department of Epidemiology, University of Michigan, School of Public Health, [2]Department of Microbiology and Immunology, [3]Department of Internal Medicine, Division of Infectious Diseases, University of Michigan, Ann Arbor, [4]Department of Public Health Sciences, and [5]Department of Medicine, Division of Infectious Diseases, Henry Ford Health System, Detroit, Michigan; and [6]Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia

Analysis Subset	Vaccinated N Pos/Total (%)	Unvaccinated N Pos/Total (%)	Unadjusted VE % (95% CI)	Adjusted VE % (95% CI)
Influenza A H3N2	57/421 (13.5)	41/203(20.2)	38 (4 to 60)	43 (5 to 66)
Age 18-49 yrs	7/77 (9.1)	20/88 (22.7)	64 (12 to 86)	67 (11 to 88)
Age 50-64 yrs	22/169 (13.0)	10/70 (14.3)	12 (-95 to 60)	10 (-127 to 64)
Age 65+ yrs	28/175 (16.0)	11/45 (24.4)	42 (-27 to 74)	48 (-33 to 80)

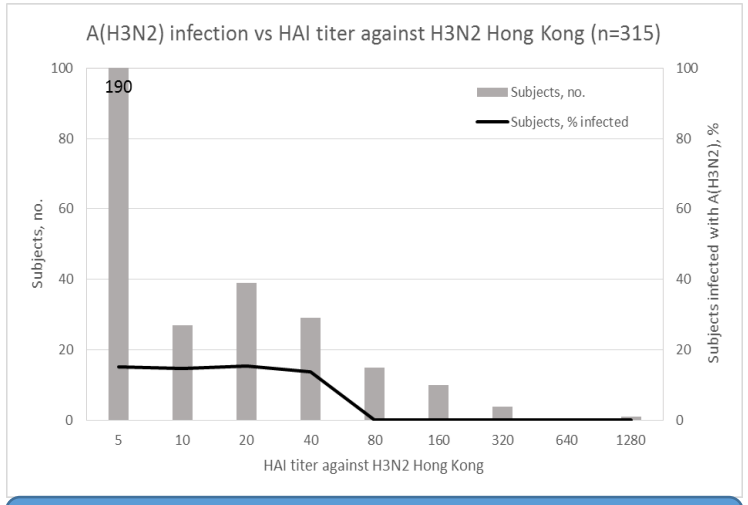
Models were adjusted for age in months (cubic spline), calendar time (categorical biweekly), sex, enrollment hospital (UM; HF), time from onset to specimen collection (days), frailty score (0-5), and Charlson score (categorical: 0, 1, 2, 3+).

In-hospital serology in a drifted year 2014-2015





VACCINE STRAIN



CIRCULATING STRAIN

Why?

- Despite mismatch between circulating and vaccine viruses, VE estimates in this study were higher than those in ambulatory care settings.
- Influenza vaccine may have been more effective in preventing severe illness requiring hospitalization.
- If vaccination reduces severity, can we see a difference between infection in vaccinated and unvaccinated individuals.

Hospitalized Adults are a Unique Population

- 90% or more have a high risk condition.
- Difficult to determine whether severity is due to the virus or due to other health problems.
- People at risk of severe disease (based on health history or chronic disease) may be admitted and treated faster.
- Major challenge for hospital-based studies of influenza.

Predictors of Severe Disease in ARI and Flu, 2014-2015 & 2015-2016

		ARI (N=1072)			Influenza A Positive (N=188)		
		ICU (OR, 95% CI)	LOS (% Change, 95% CI)	30 Day Readmission (OR, 95% CI)	ICU (OR, 95% CI)	LOS (% Change, 95% CI)	30 Day Readmission (OR, 95% CI)
Male Sex		1.5 (1.0, 2.2)	6.1 (-0.5, 13.1)	1.1 (0.8, 1.6)	0.7 (0.3, 1.8)	-5.0(-19.2, 11.7)	0.4 (0.1, 1.4)
Age	**18-49**	1.0	0.0	1.0	1.0	0.0	1.0
	50-64	1.0 (0.6, 1.6)	3.6 (-4.4, 12.3)	0.9 (0.6, 1.3)	1.1 (0.3, 3.6)	3.2 (-16.1, 26.9)	1.5 (0.3, 7.7)
	≥65	1.0 (0.6, 1.6)	0.4 (-7.7, 9.1)	0.6 (0.4, 1.0)	1.0 (0.3, 3.4)	6.6 (-13.8, 31.9)	1.2 (0.3, 6.2)
Charlson Score ≥2		1.5 (1.0, 2.3)	21.7 (13.3, 30.7)	1.8 (1.2, 2.7)*	1.6 (0.5, 5.7)	8.5 (-11.0, 32.2)	1.1 (0.3, 4.2)
Vaccination		-	-	-	1.0 (0.3, 3.1)	-6.1 (-22.4, 13.6)	0.9 (0.3, 3.5)
Frailty Score		1.5 (0.8, 3.0)	22.7 (9.3, 37.5)*	1.4 (0.8, 2.5)	1.0 (0.1, 6.1)	31.4 (-4.5, 80.9)	8.9 (1.2, 78.0)*

[1]Adjusted models contain male sex, age group, enrollment site, Charlson score, weighted frailty score, total annual healthcare visits, and influenza status. Influenza A subtype and vaccination were also included in models restricted to influenza A positive adults.

Segaloff HE et al. Epidemiology and Infection, 2018, 146, 1350-1358.

Time to Discharge and Antiviral Treatment

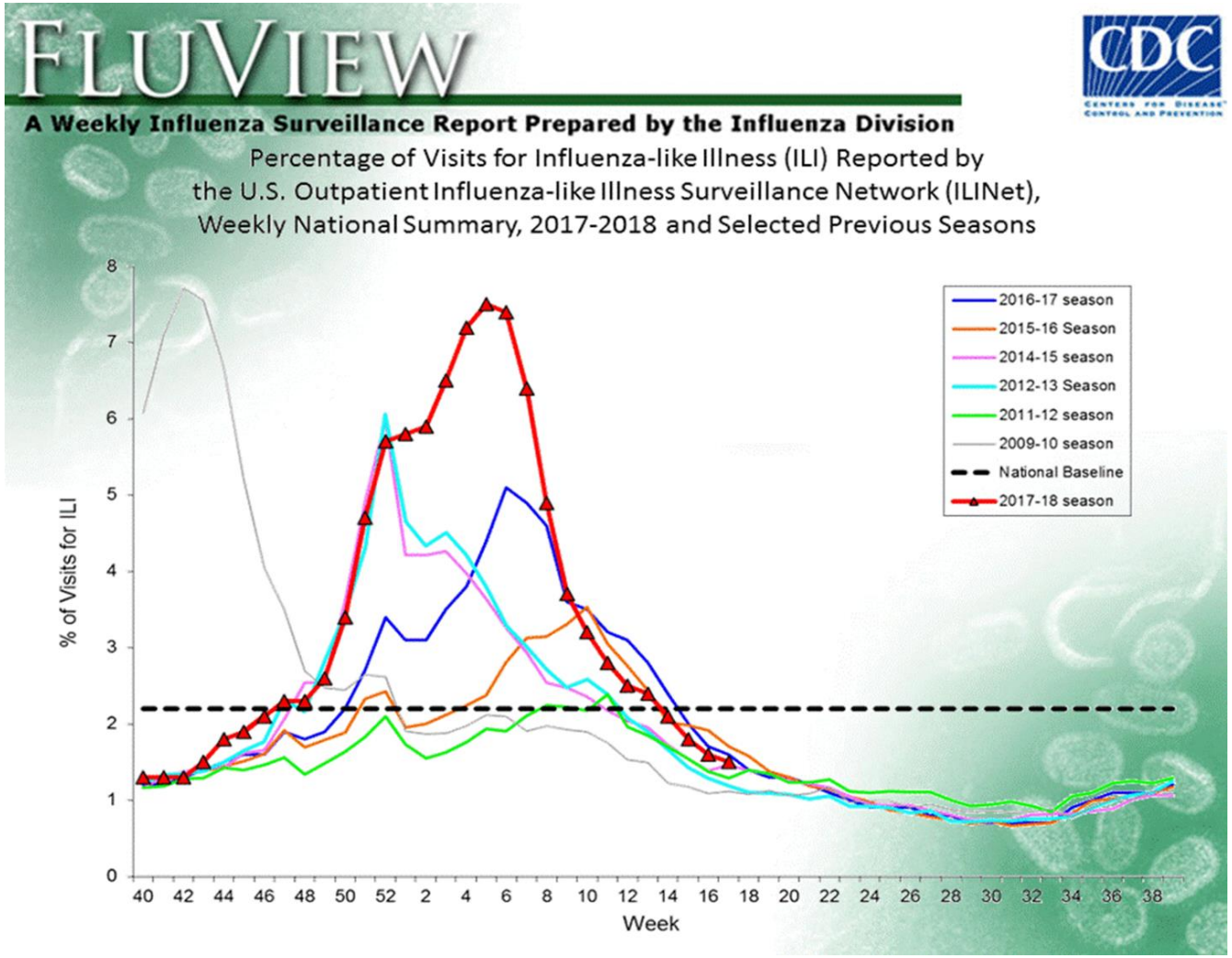
	Overall (N=201)		Vaccinated (N=106)		Unvaccinated (N=95)	
Predictors	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P
Antiviral Treatment	1.1 (0.8, 1.5)	0.44	1.6 (1.0, 2.4)	0.04	0.9 (0.5, 1.4)	0.52
Weighted Frailty Score	0.5 (0.3, 1.0)	0.04	0.6 (0.3, 1.3)	0.17	0.5 (0.2, 1.2)	0.11
Total Visits (Tertiles)						
Tertile 0	ref		Ref		ref	
Tertile 1	1.6 (1.0, 2.7)	0.05	0.5 (0.1, 1.6)	0.23	1.6 (0.9, 2.9)	0.09
Tertile 2	1.3 (0.8, 2.1)	0.32	0.3 (0.1, 1.0)	0.05	1.3 (0.7, 2.4)	0.40
Tertile 3	1.5 (0.9, 2.4)	0.13	0.4 (0.2, 1.2)	0.09	1.6 (0.8, 3.5)	0.21

[1]Models contain all predictors in the table

What we've learned…

- LAIV
- Vaccination and Severity of Illness
- Egg-Adaptations in the Influenza Vaccine

2017-2018 Influenza Season, US Data



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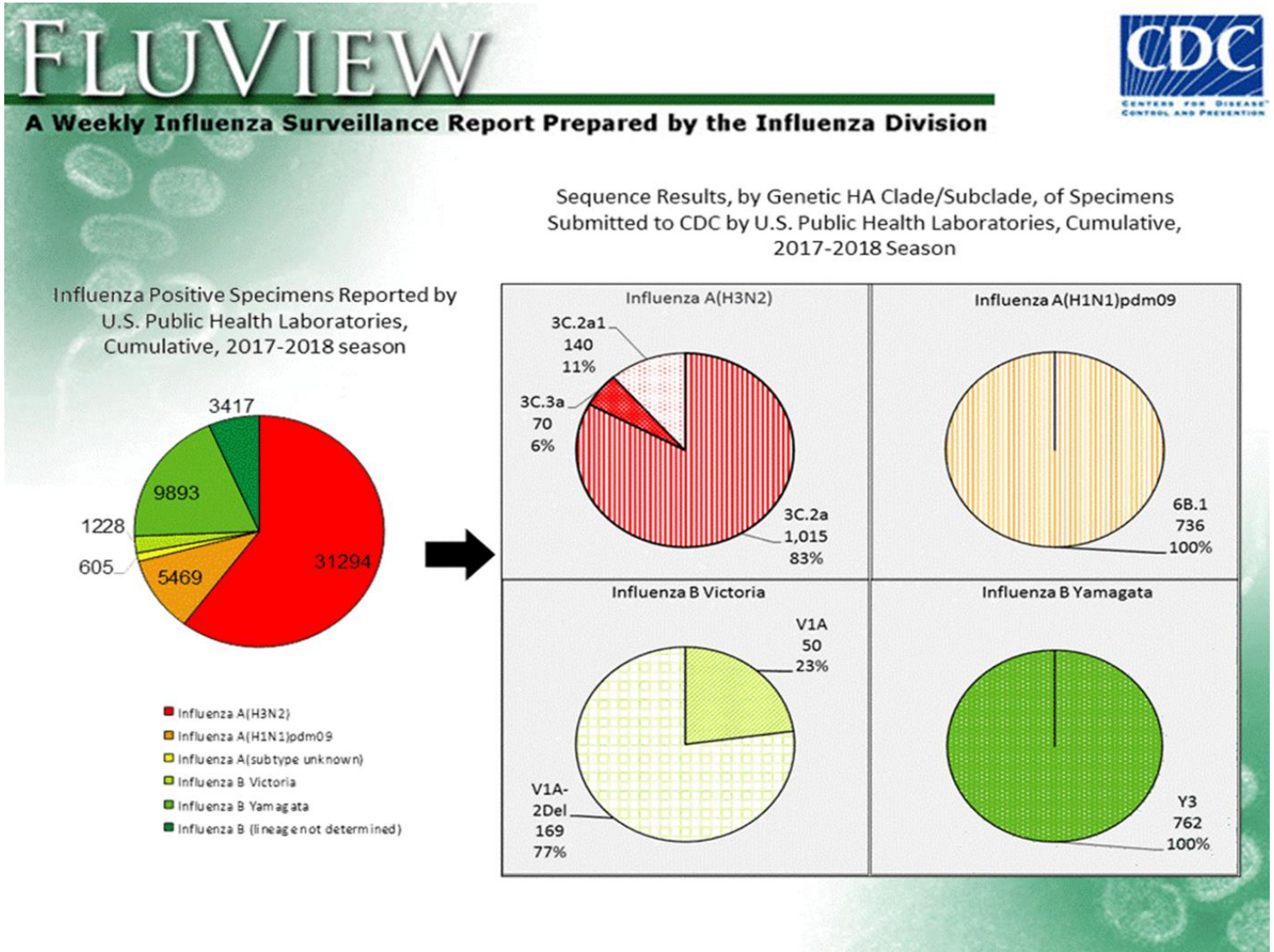
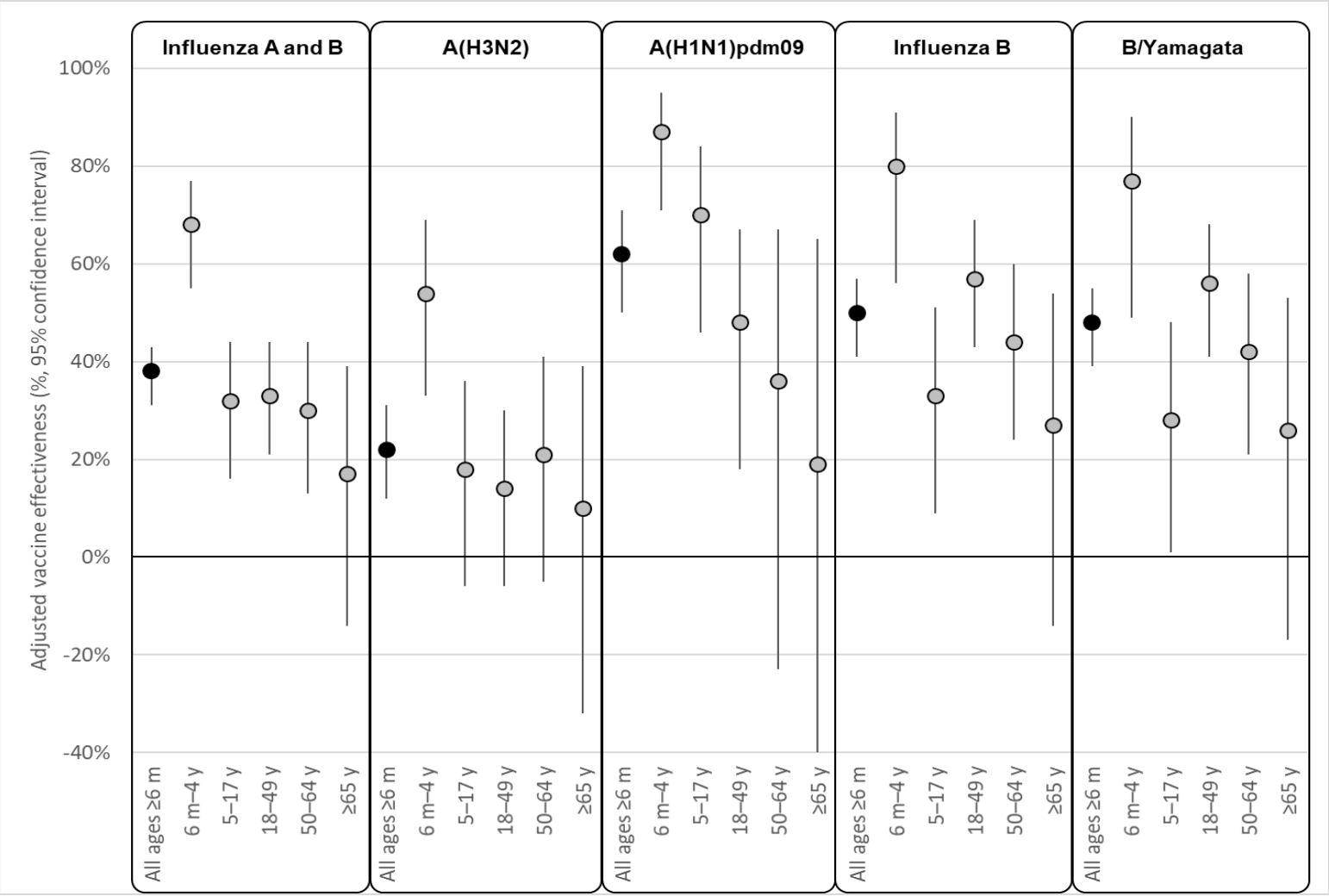
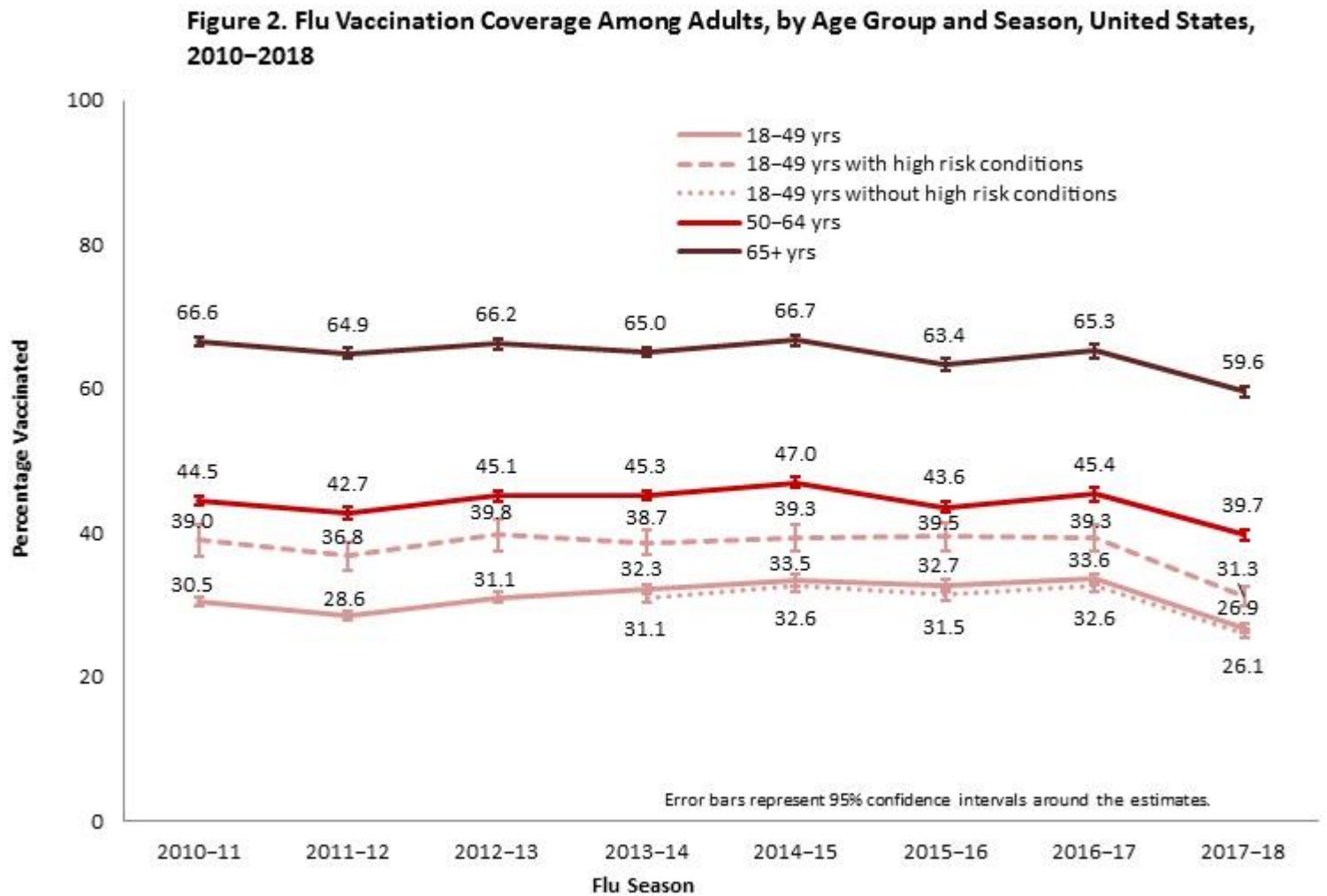


Adjusted vaccine effectiveness against outpatient medically-attended influenza-associated illness, US Flu VE Network — 2017–2018 influenza season



Rolfes et al. Clin Infect Dis, Under Review

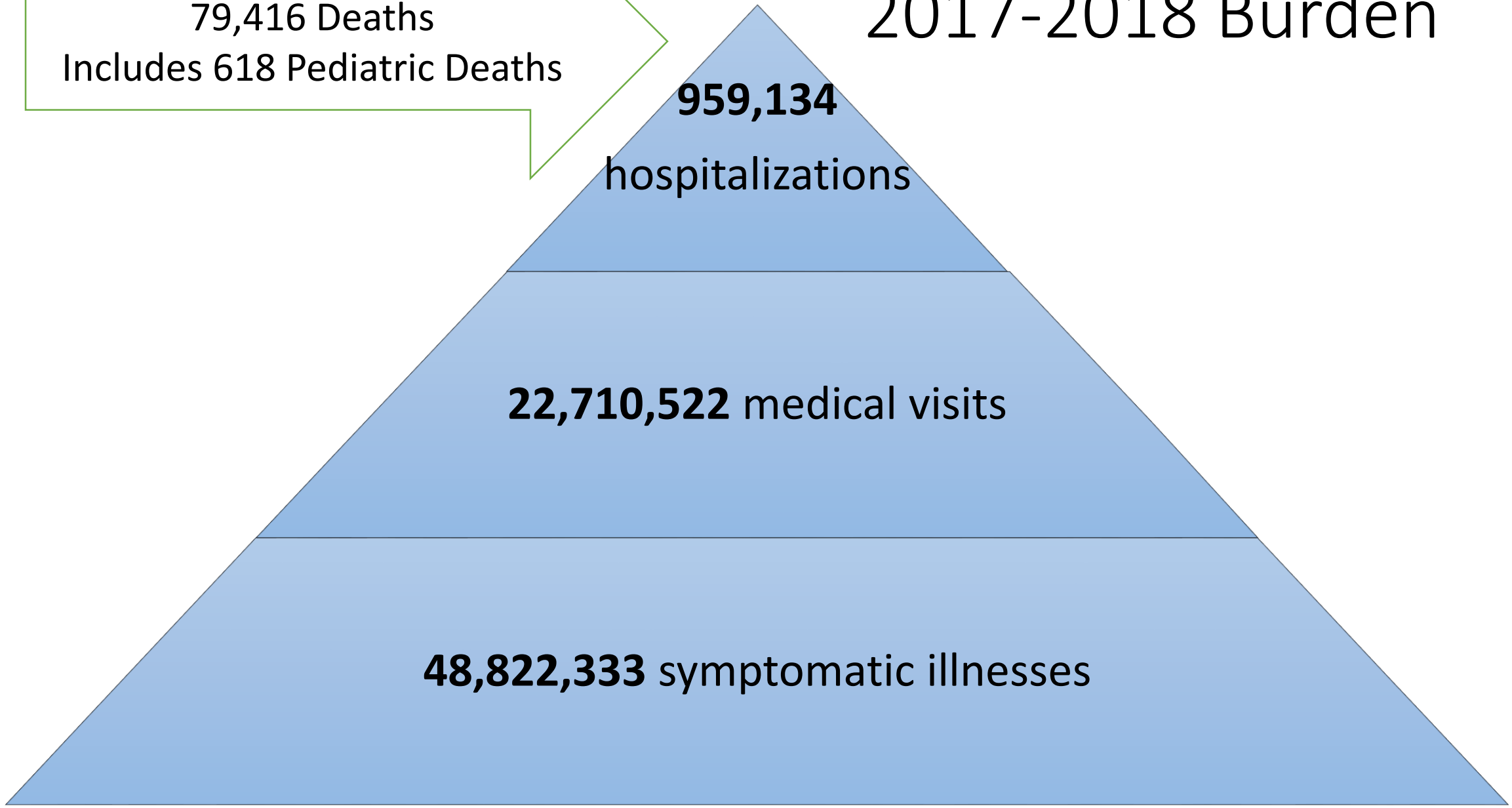
Vaccine use was down in 2017-2018



www.cdc.gov/flu/fluvaxview

2017-2018 Burden

79,416 Deaths
Includes 618 Pediatric Deaths



the **burden** of **flu** disease 2017 - 2018

The estimated number of flu **illnesses** during the 2017-2018 season:

49 million

More than the combined populations of Texas and Florida

The estimated number of flu **hospitalizations** during the 2017-2018 season:

960,000

More than the number of staffed hospital beds in the U.S.

The estimated number of flu **deaths** during the 2017-2018 season:

79,000

More than the average number of people who attend the Super Bowl each year

DATA: Influenza Division program impact report 2017-2018, https://www.cdc.gov/flu/about/burden/index.html

CDC

get **vaccinated**
www.cdc.gov/flu

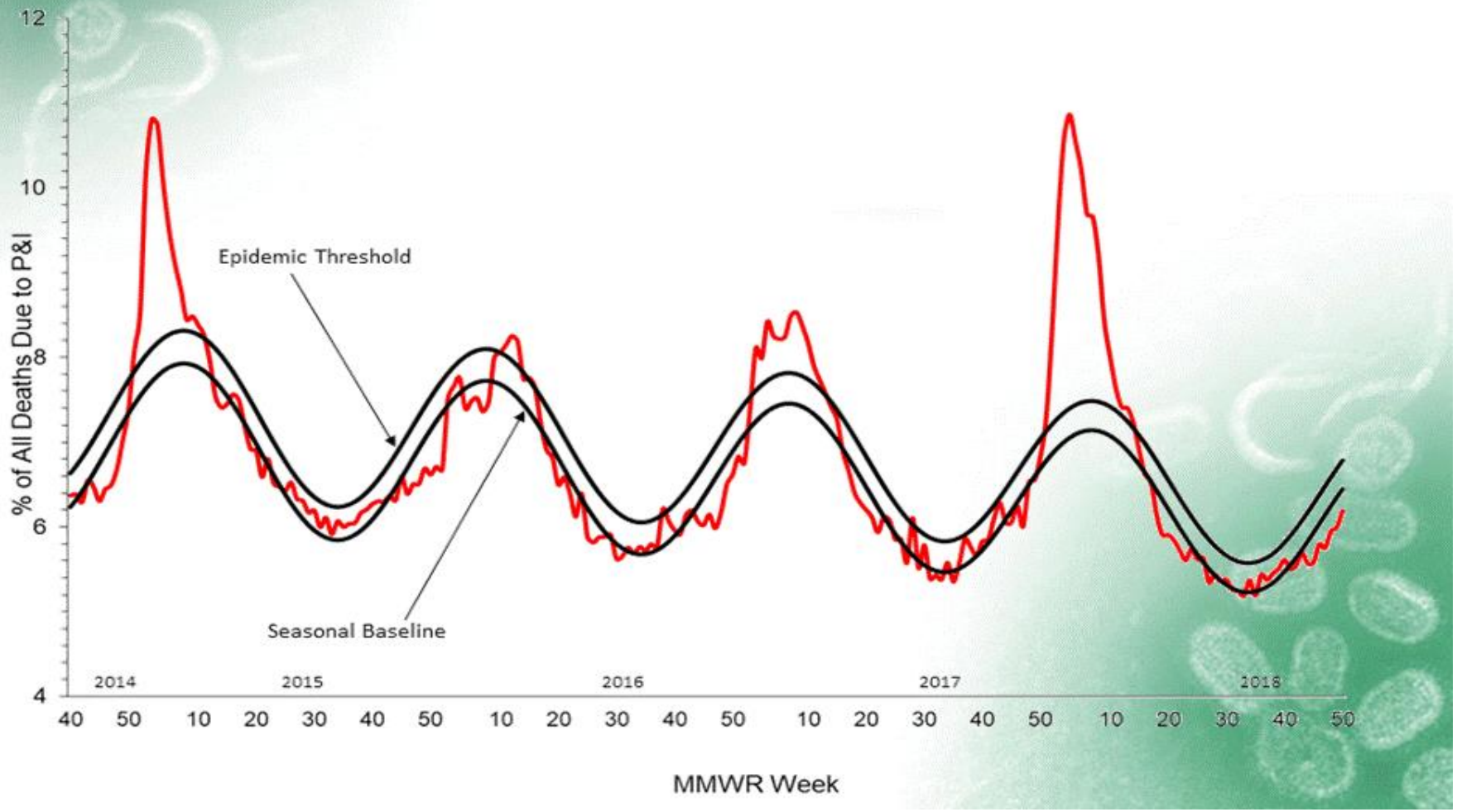
FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

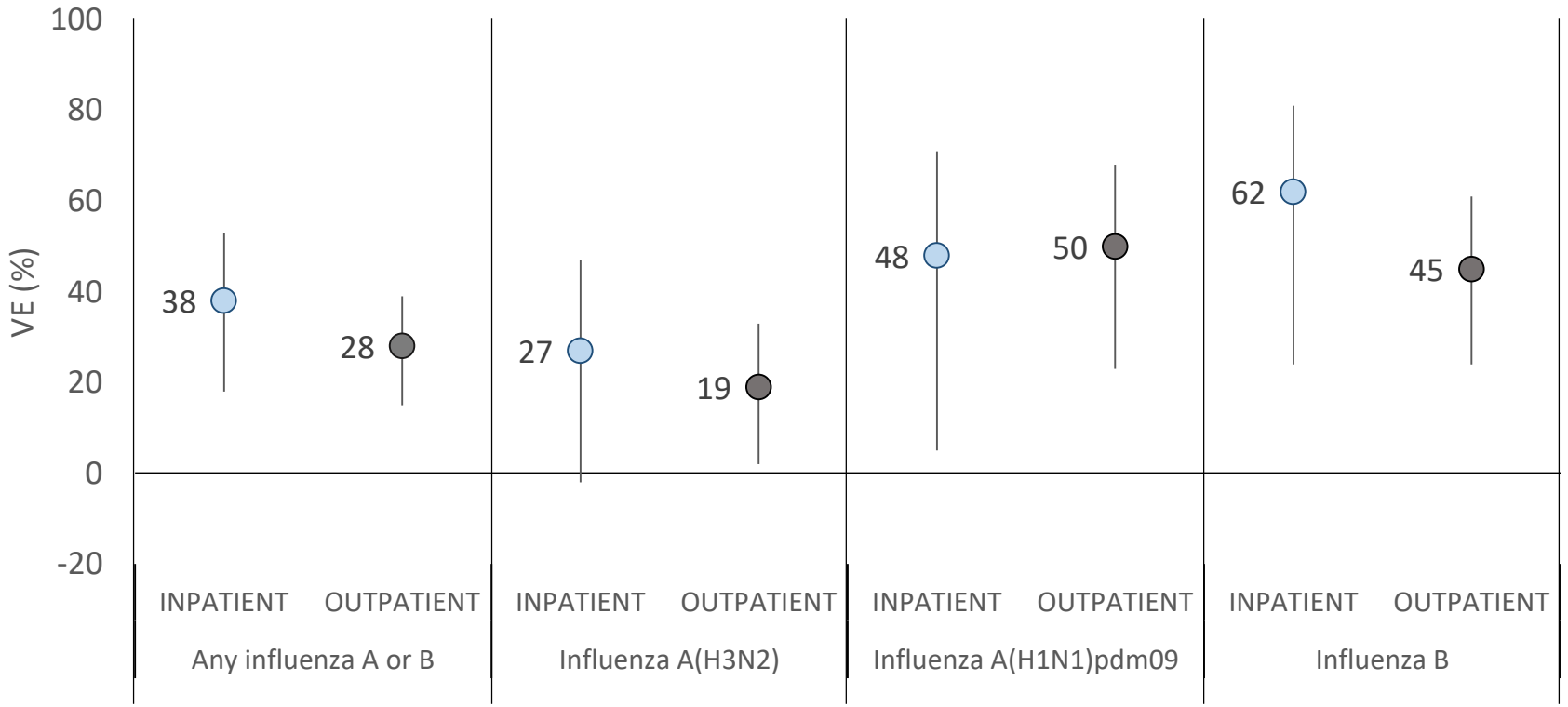
CDC
Centers for Disease Control and Prevention

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

Data through the week ending December 15, 2018, as of December 27, 2018



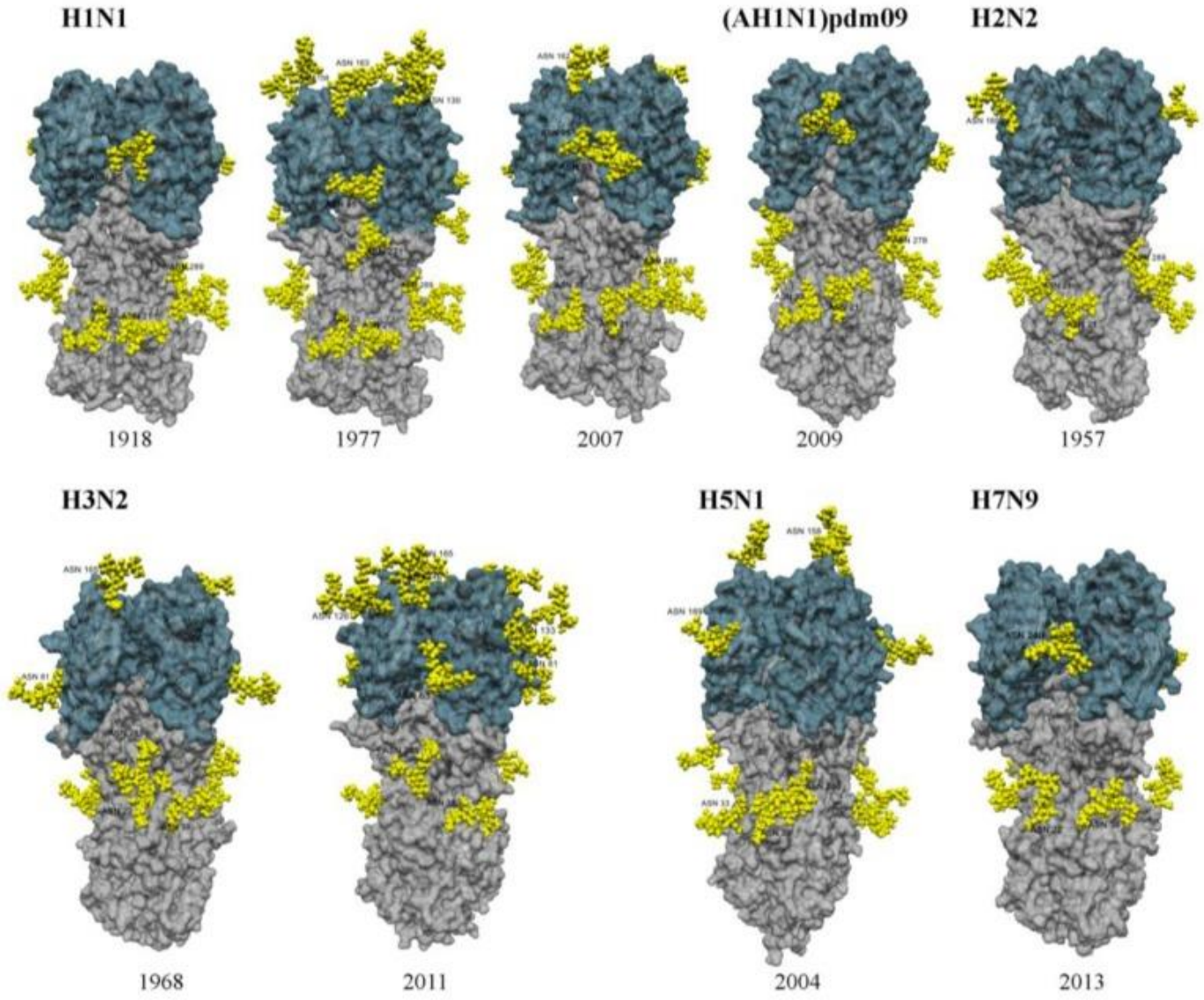
2017-18 Interim* VE Estimates: Inpatient vs Outpatient VE among adults ≥18 years



*US Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN) enrollment though January 20, 2018 (n=1562); US Flu VE Network enrolment through February 3, 2018 (n=2876)

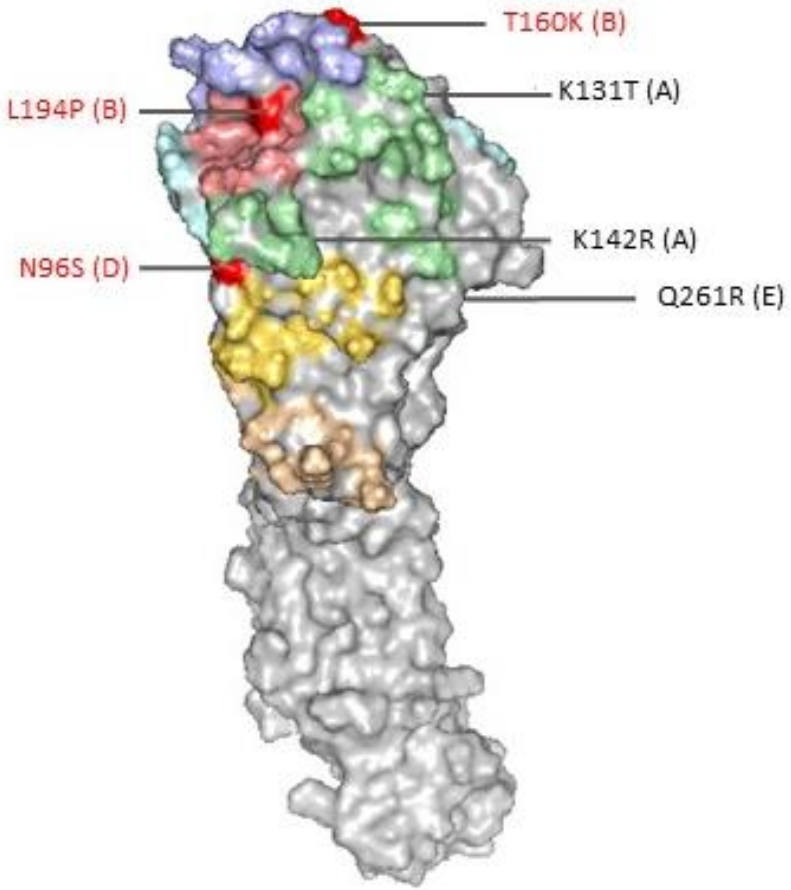
2017-2018 and the case of the egg-adaptation

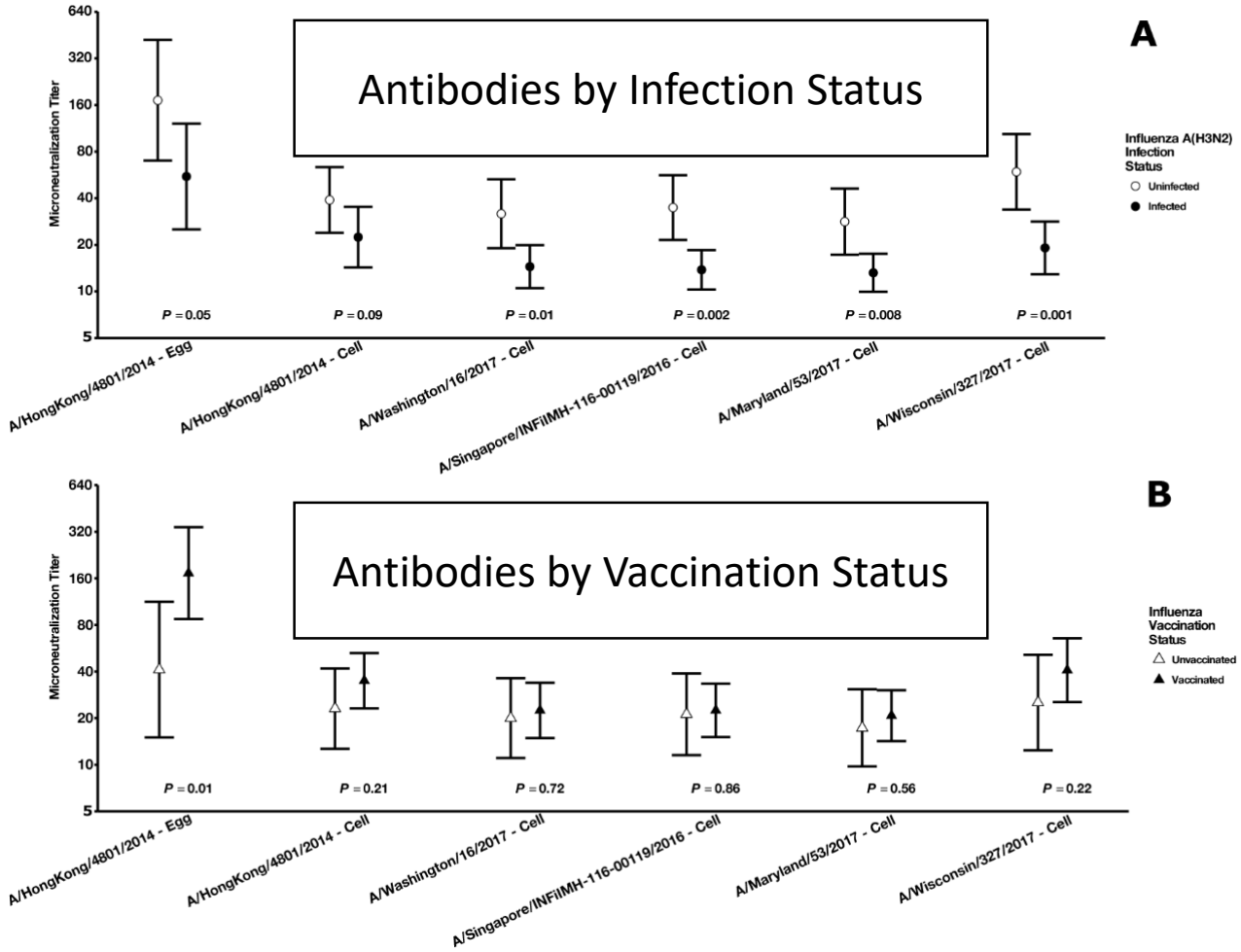
Glycosylation sites change with drift.



Tate MD et al. Playing Hide and Seek: How Glycosylation of the Influenza Virus Hemagglutinin Can Modulate the Immune Response to Infection. Viruses 2014, 6, 1294-1316.

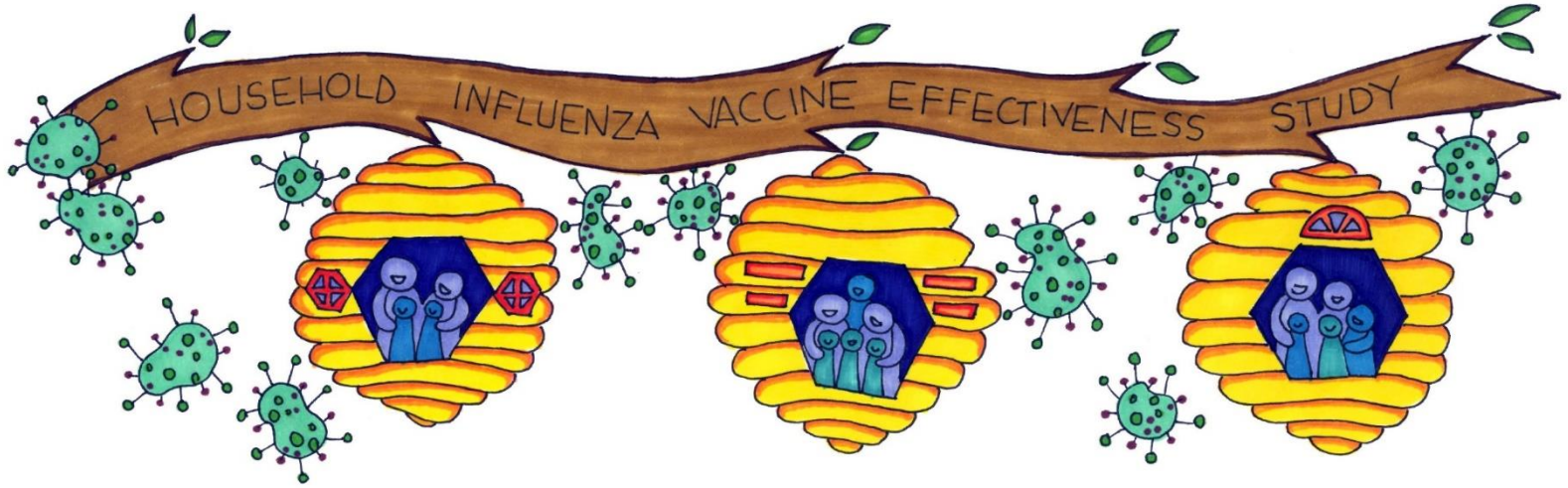
Egg Adaptations in Recent H3N2 strains

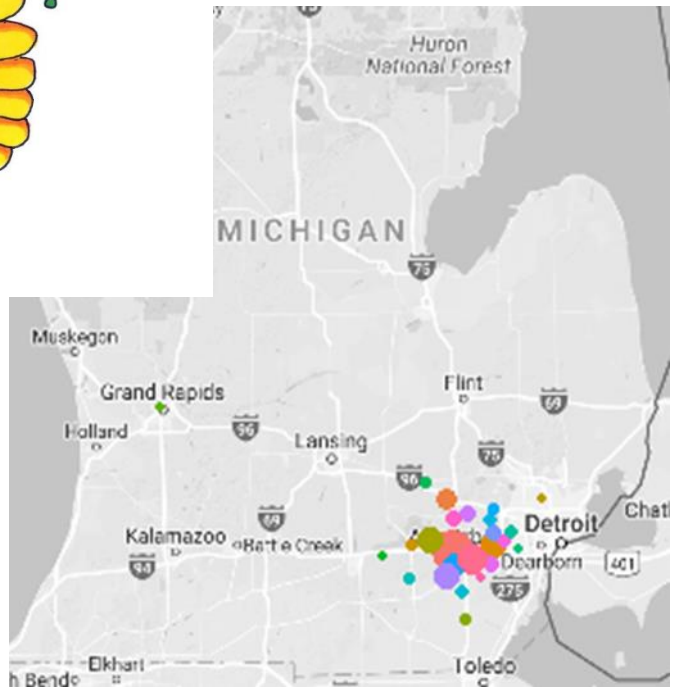




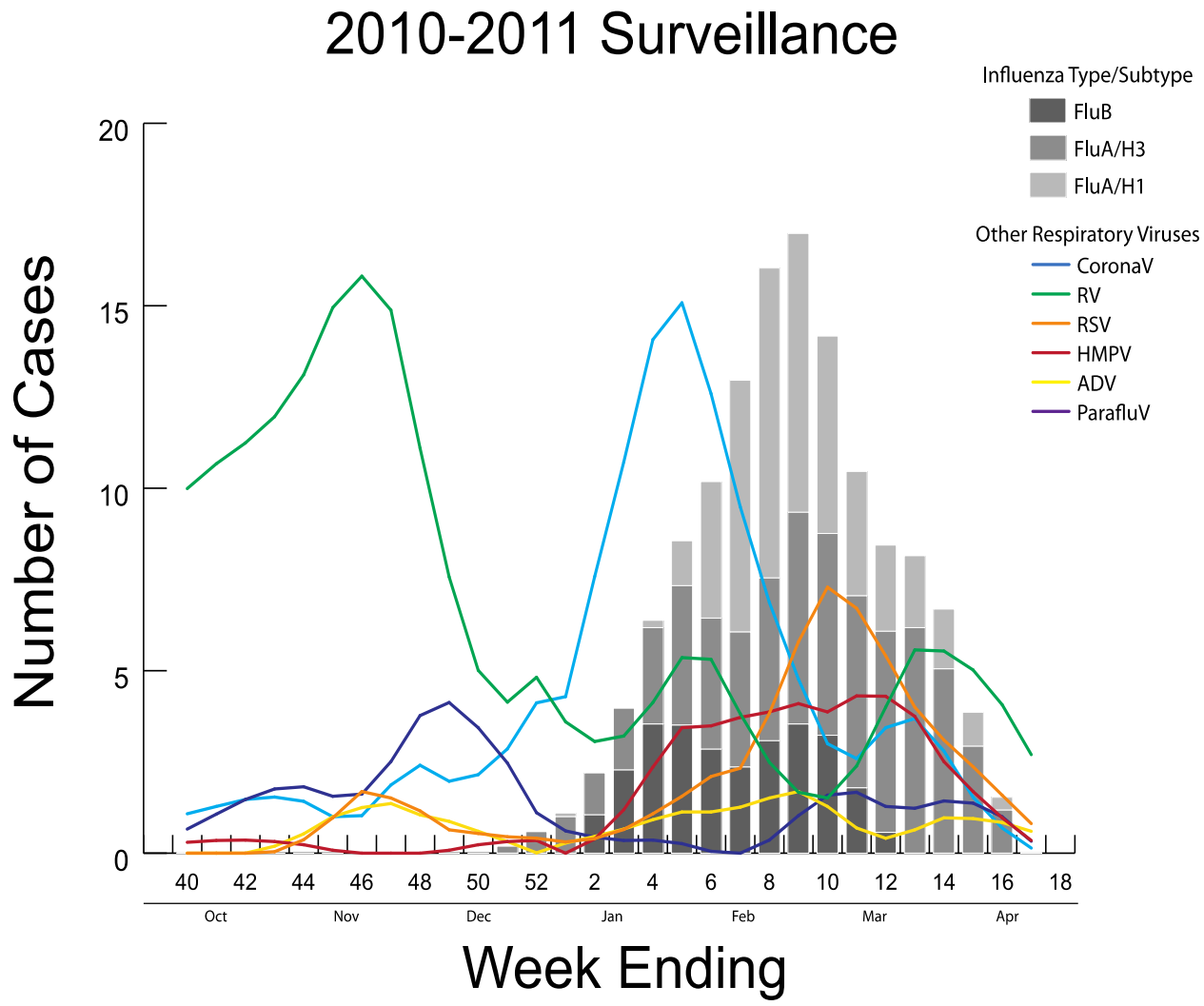
Levine M, Martin ET, et al. J Infect Dis. In press.

What else can we learn?





HIVE Surveillance



2018-2019 Influenza Season, US Data

TABLE 1. Influenza test results and seasonal vaccination status among patients with medically attended acute respiratory illness (N = 3,254), by selected characteristics — U.S. Influenza Vaccine Effectiveness Network, November 23, 2018—February 2, 2019*

Characteristic	Test result status			Vaccination status†		
	Influenza-positive no. (%)	Influenza-negative no. (%)	P-value§	No. of patients	Vaccinated No. (%)	P-value§
Overall	**465 (14)**	**2,789 (86)**	—	**3,254**	**1,789 (55)**	—
Study site						
Michigan	76 (15)	438 (85)	0.006	514	314 (61)	<0.001
Pennsylvania	101 (17)	511 (83)		612	335 (55)	
Texas	72 (10)	637 (90)		709	327 (46)	
Washington	171 (16)	915 (84)		1,086	647 (60)	
Wisconsin	45 (14)	288 (86)		333	166 (50)	

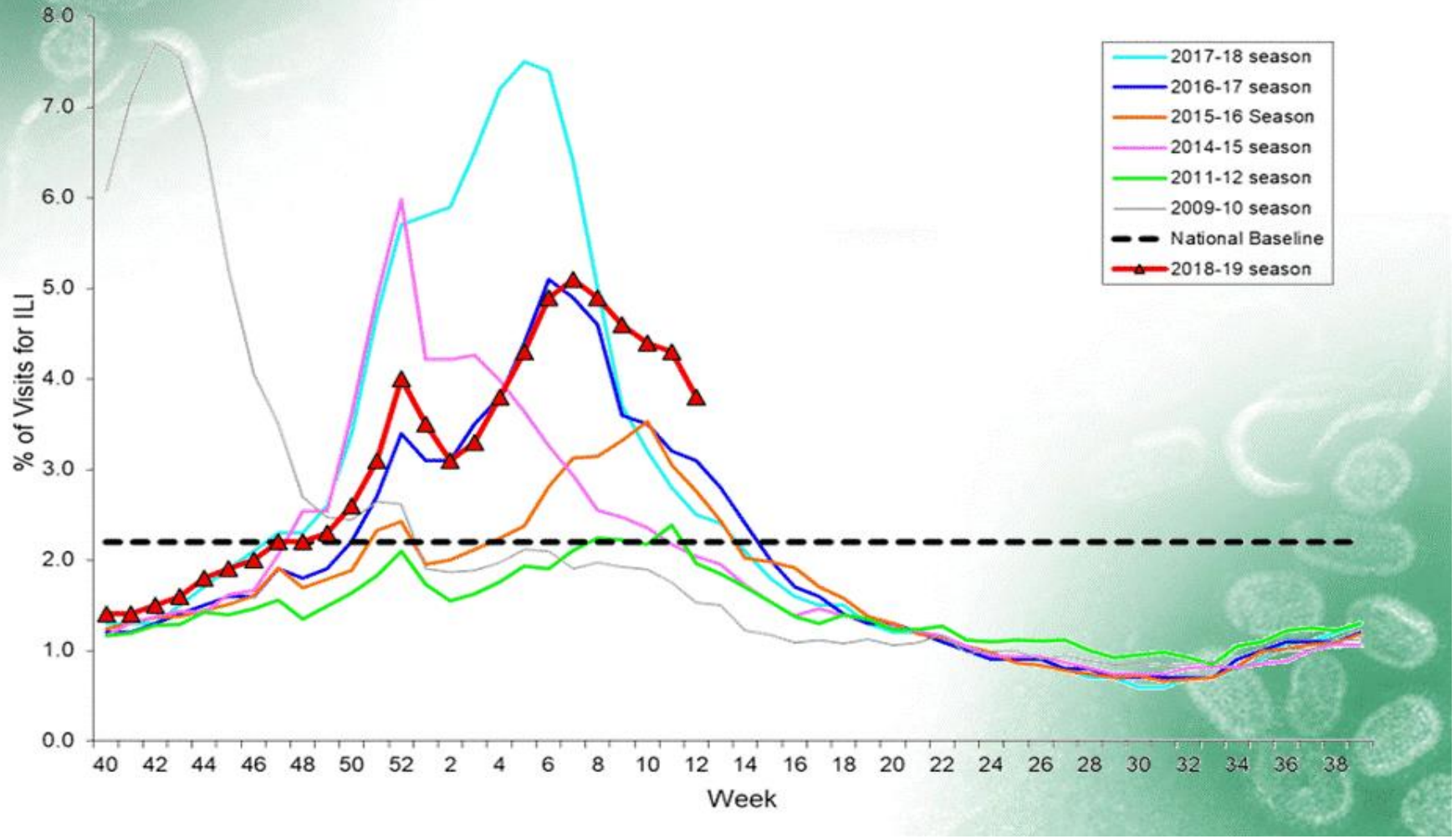
TABLE 2. Number and percentage outpatients with acute respiratory illness and cough (N = 3,254) receiving 2018–19 seasonal influenza vaccine, by influenza test result status, age group, and vaccine effectiveness* against all influenza A and B and against virus type A(H1N1)pdm09 — U.S. Influenza Vaccine Effectiveness Network, November 23, 2018–February 2, 2019

	Influenza-positive		Influenza-negative		Vaccine effectiveness*	
Influenza type/Age group	Total	Vaccinated no. (%)	Total	Vaccinated no. (%)	Unadjusted % (95% CI)	Adjusted % (95% CI)†
Influenza A and B						
Overall	**465**	198 (43)	**2,789**	1,591 (57)	44 (32 to 54)	47 (34 to 57)§
Age group						
6 mos–17 yrs	**173**	58 (34)	**926**	515 (56)	60 (43 to 71)	61 (44 to 73)§
18–49 yrs	**166**	58 (35)	**932**	403 (43)	30 (1 to 50)	37 (9 to 56)§
≥50 yrs	**126**	82 (65)	**931**	673 (72)	29 (-6 to 52)	24 (-15 to 51)
Influenza A(H3N2)						
Overall	**101**	42 (42)	**2,789**	1,591 (57)	46 (20 to 64)	44 (13 to 64)§
Influenza A(H1N1)pdm09						
Overall	**293**	125 (43)	**2,789**	1,591 (57)	44 (29 to 56)	46 (30 to 58)§
Age group						
6 mos–17 yrs	**106**	37 (35)	**926**	515 (56)	57 (35 to 72)	62 (40 to 75)§
18–49 yrs	**113**	38 (34)	**932**	403 (43)	33 (0 to 56)	45 (14 to 64)§
≥50 yrs	**74**	50 (68)	**931**	673 (72)	20 (-33 to 52)	8 (-59 to 46)

FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, 2018-2019 and Selected Previous Seasons

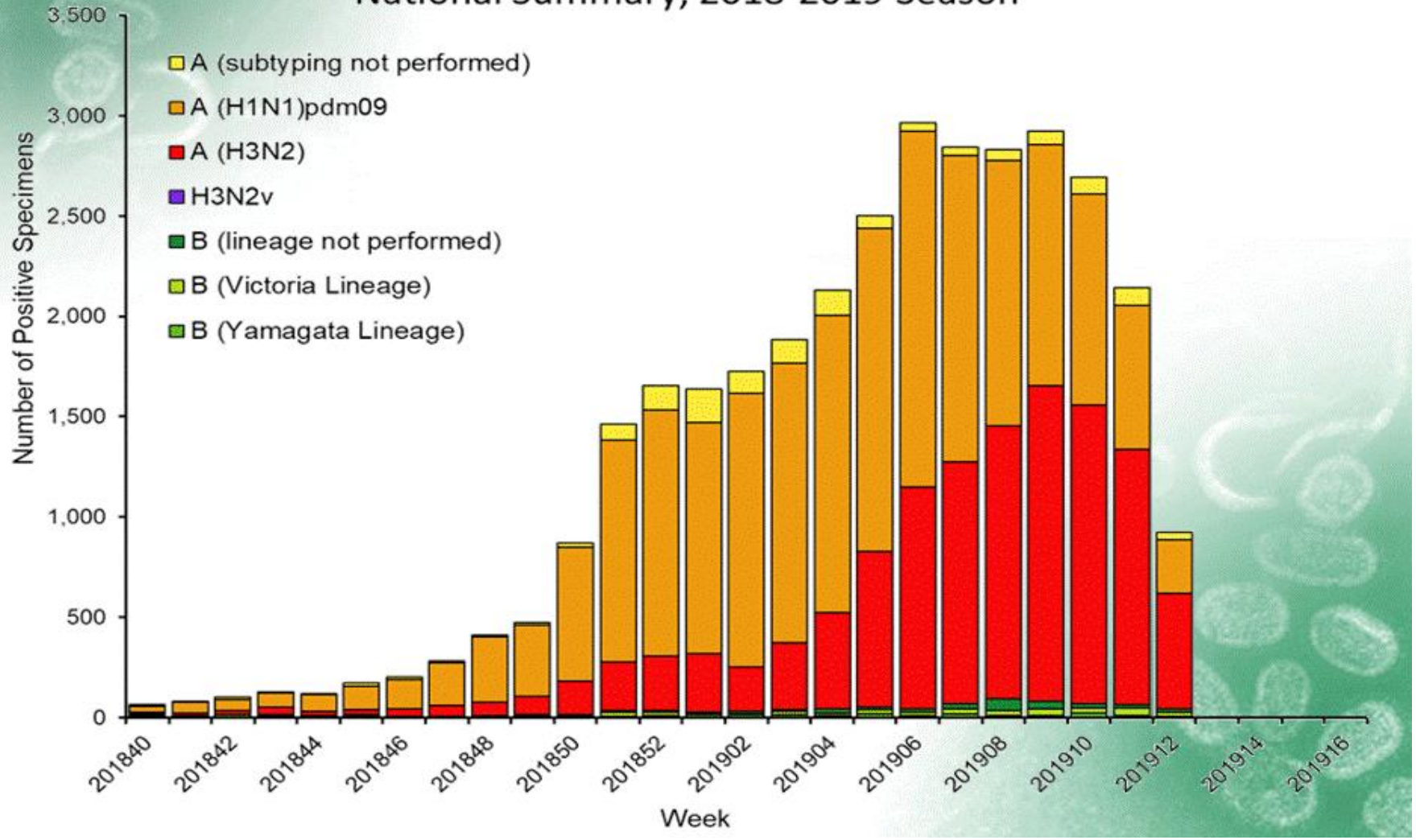


FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

CDC
Centers for Disease Control and Prevention

Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, National Summary, 2018-2019 Season

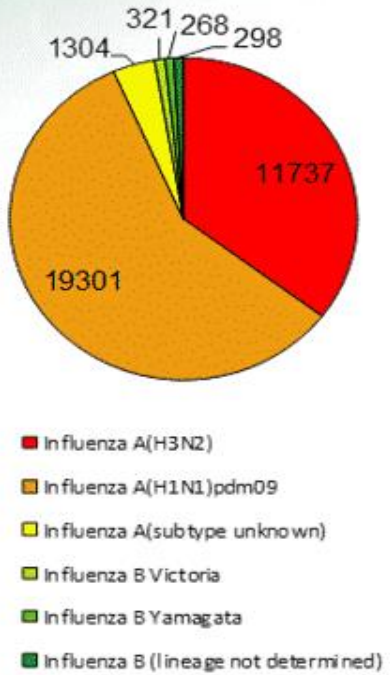


FLUVIEW

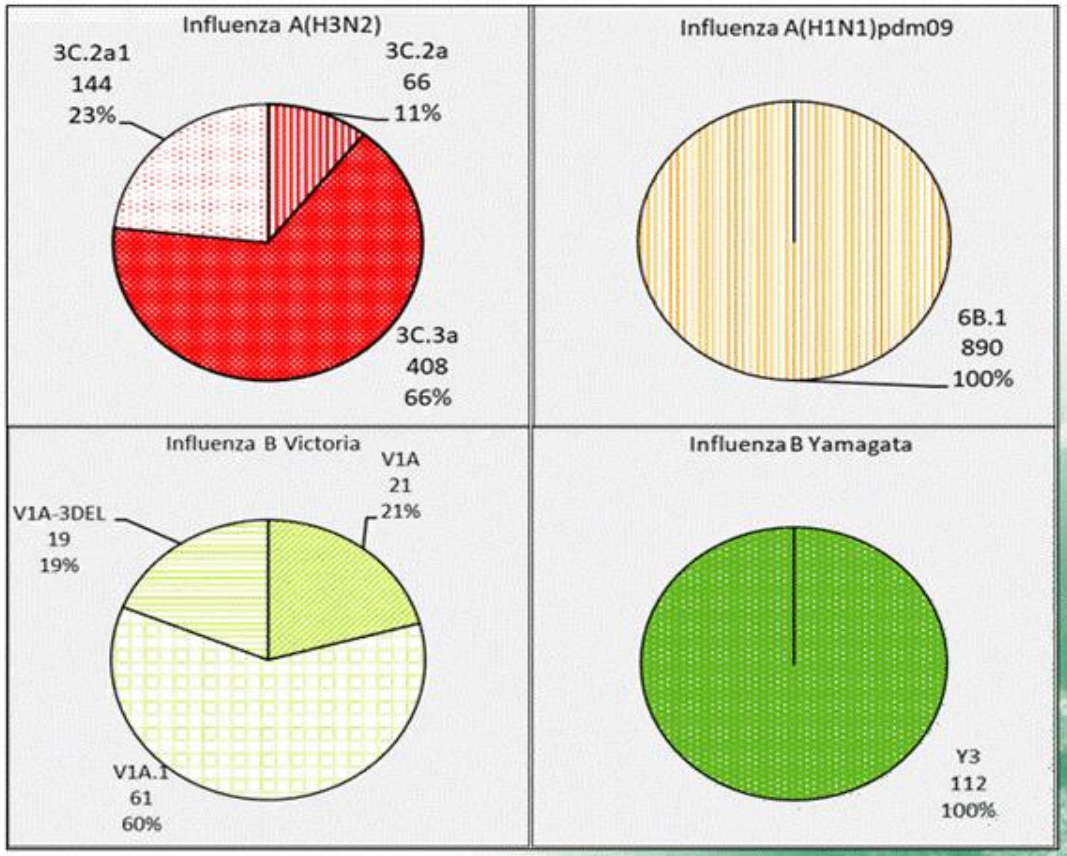
A Weekly Influenza Surveillance Report Prepared by the Influenza Division

CDC
Centers for Disease Control and Prevention

Influenza Positive Specimens Reported by U.S. Public Health Laboratories, Cumulative, 2018-2019 Season

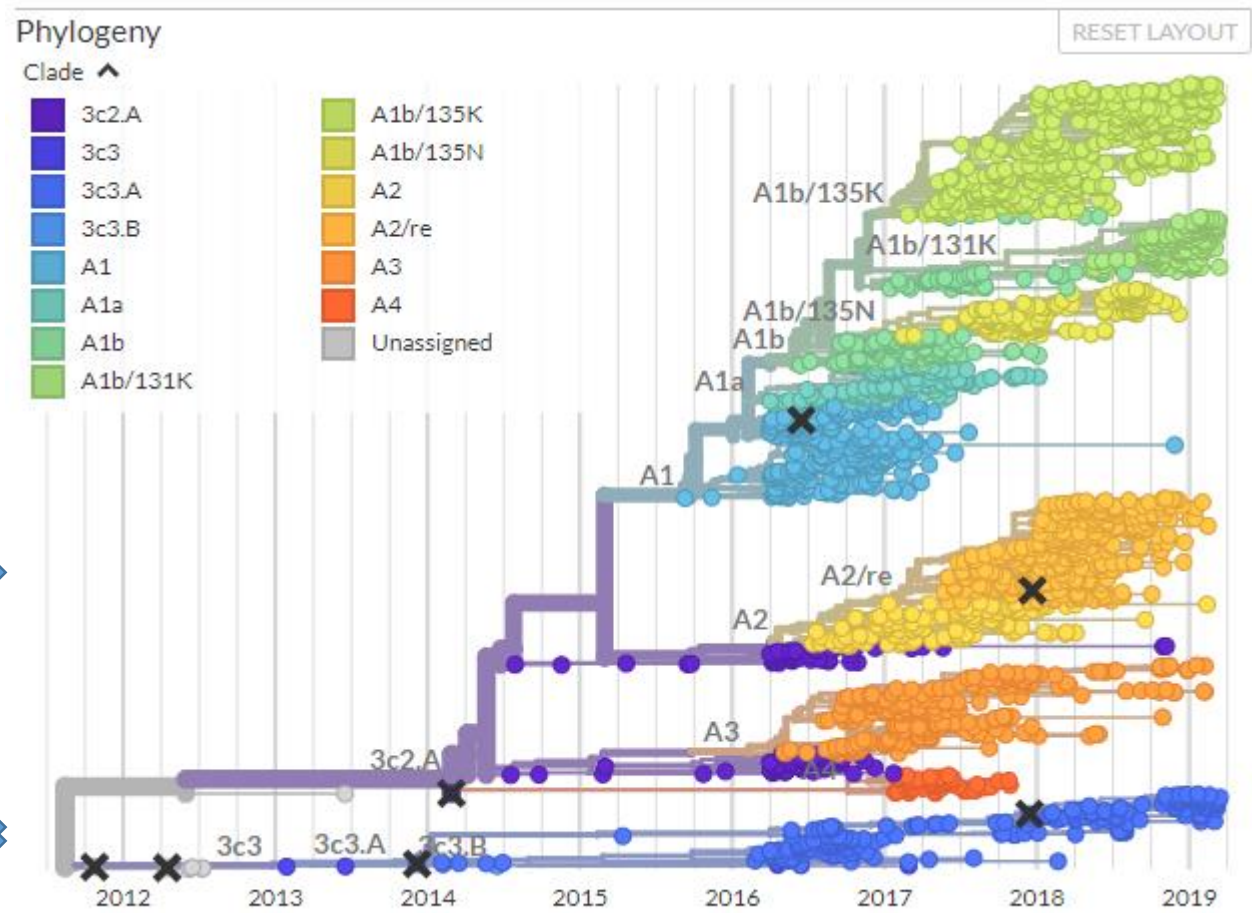


Sequence Results, by Genetic HA Clade/Subclade, of Specimens Submitted to CDC by U.S. Public Health Laboratories, Cumulative, 2018-2019 Season



Real-time tracking of influenza A/H3N2 evolution

Showing 2175 of 2175 genomes sampled between Oct 2011 and Mar 2019 and comprising 15 clade memberships, 10 regions, 117 countries and 37 authors.

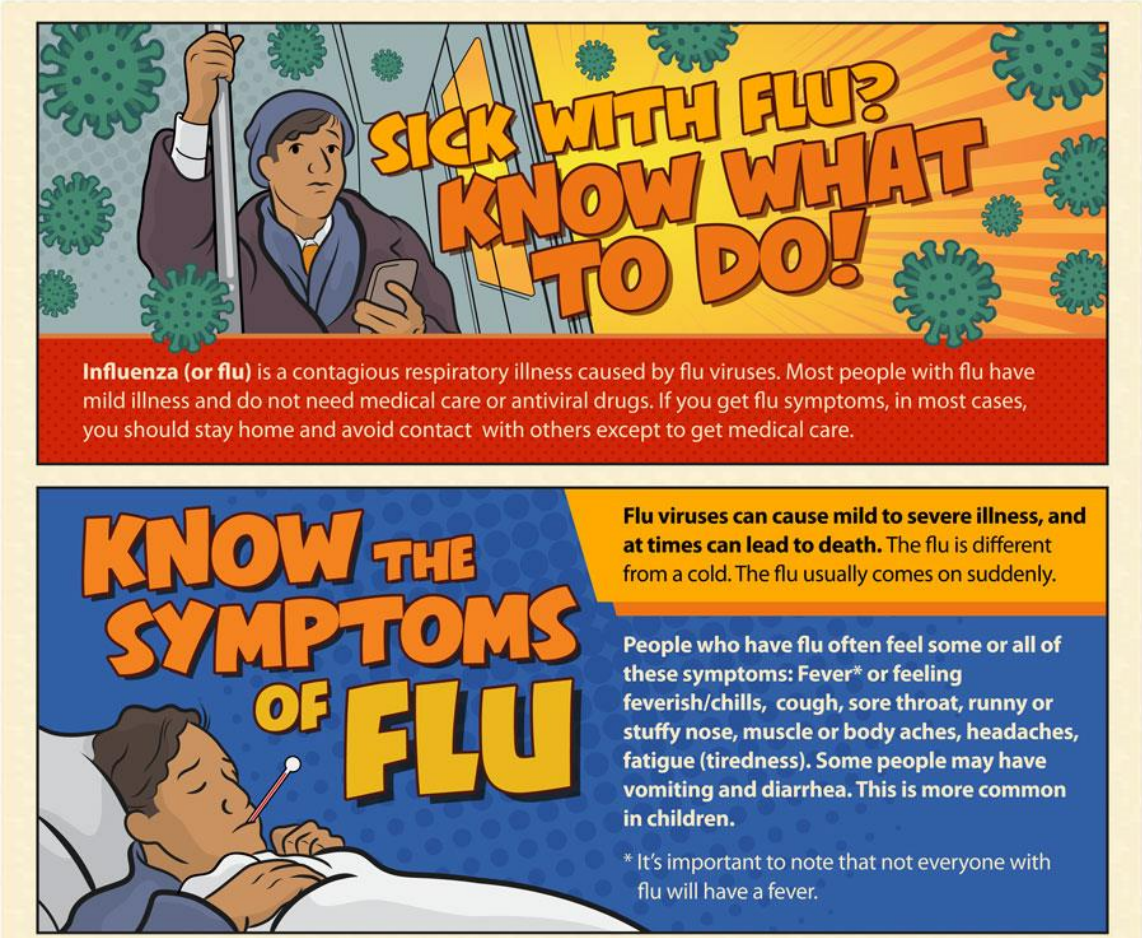


2018-2019 Vaccine

2019-2020 Vaccine Strain

Nextstrain.org/flu

Vaccination isn't the only tool



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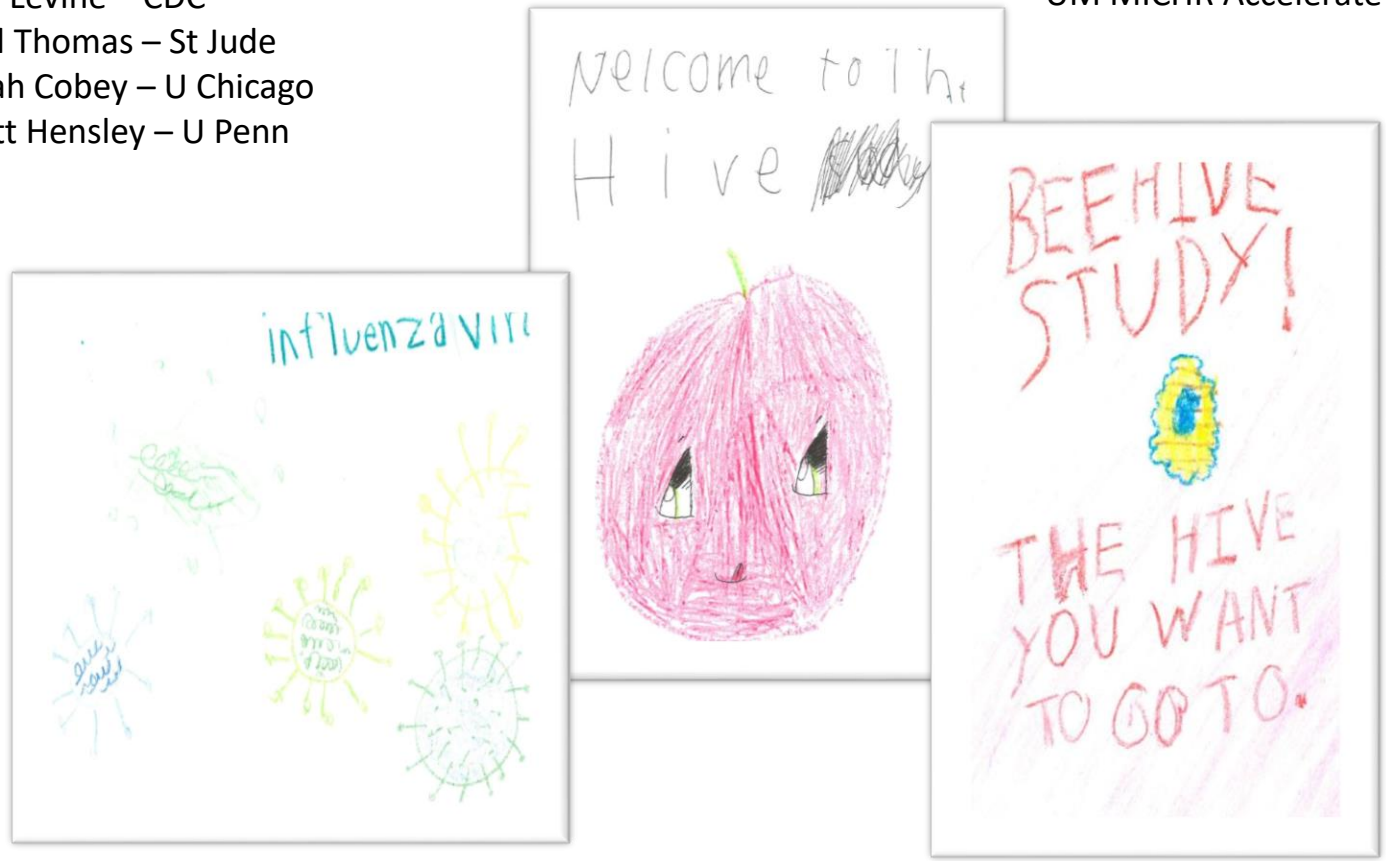
CEIRS: SJCEIRS Subcontract HHSN2722014400006C
UM MICHR Accelerate Award



Influenza Images: CDC Public Health Image Library

Participants and HIVE Study Households

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Thank you!

Questions?

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