Influenza Updates

28APR2018

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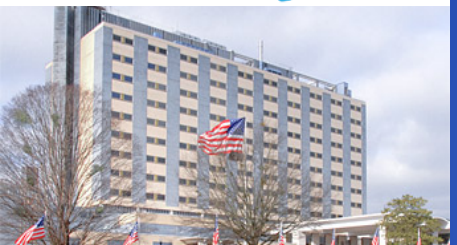
GEORGIA EIP emerging infections program



EMORY UNIVERSITY SCHOOL OF MEDICINE

VACCINE & TREATMENT EVALUATION UNIT

Children's Healthcare of Atlanta

POTENTIAL CONFLICTS AND DISCLOSURES

- Clinical Trials
  - MedImmune
  - Regeneron
  - PaxVax
- I have served as consultant for Abbvie (Palivizumab)
- RSV-related epidemiological research
  - MedImmune
  - Novavax
  - Pfizer
- Funding for Influenza and RSV-related research from both CDC and NIH

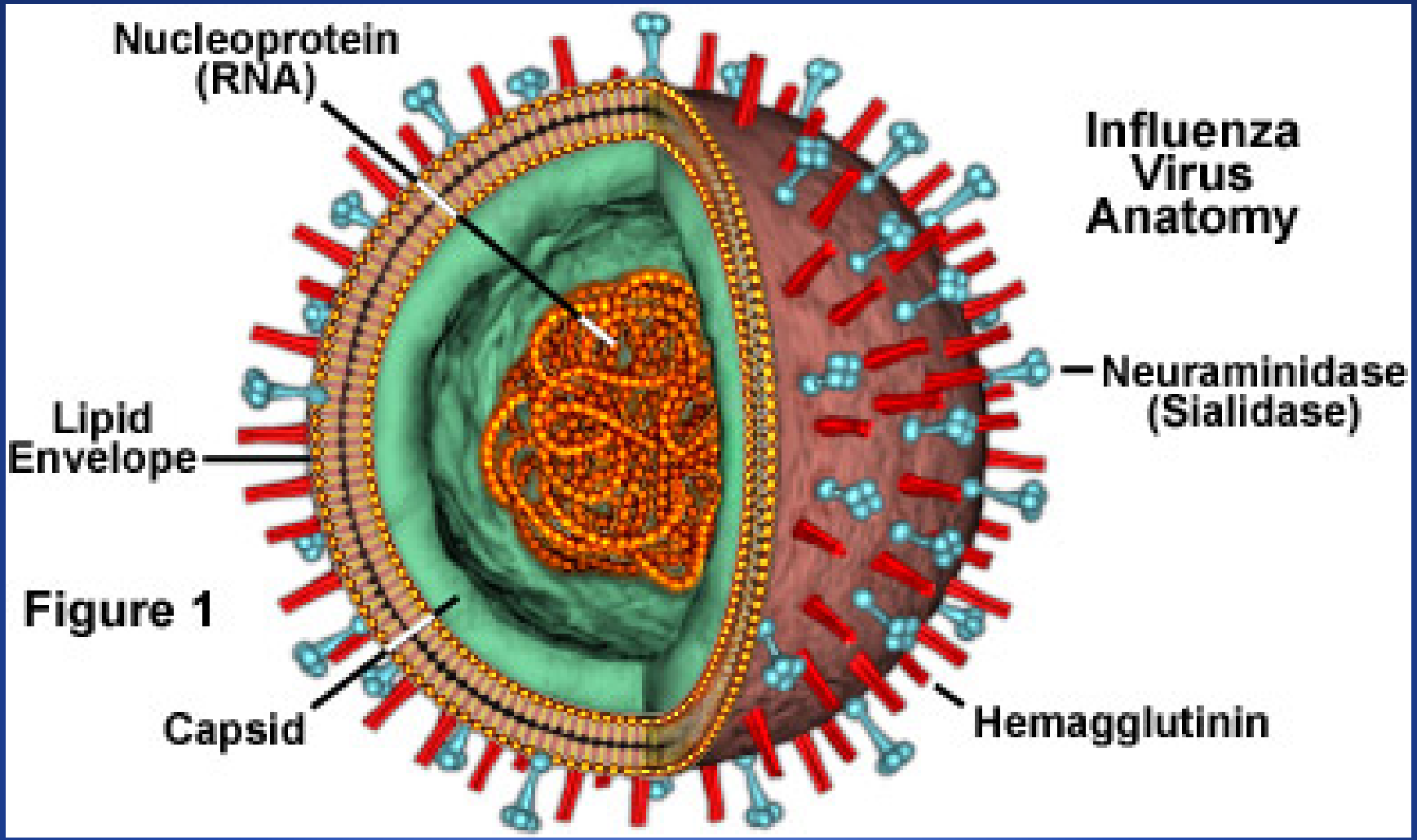
Learning Objectives

1. To better describe influenza epidemiology.

2. To understand the benefits and limitations of influenza vaccination.

3. To understand the potential for influenza pandemics and the current pandemic threats.

Influenza



Usually H3N2, H1N1, 2009H1N1, B (Victoria), B (Yamagata)

Occasionally from animals (H5N1, H3N2varient, H7N9)

Seasonal influenza epidemiology

Describe this Influenza Season (1 WORD)!

PollEverywhere 2 WORD ASSOCIATION

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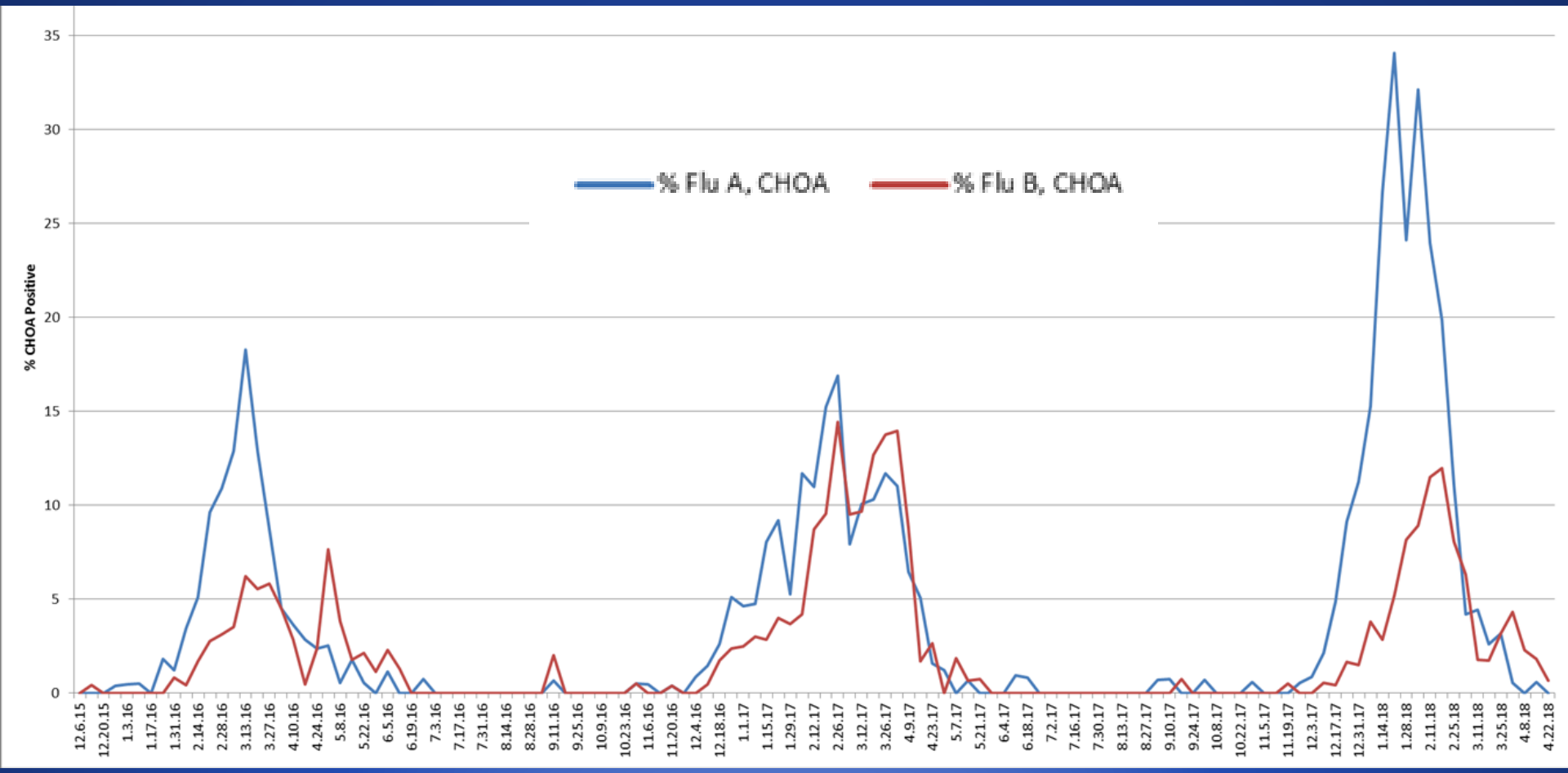
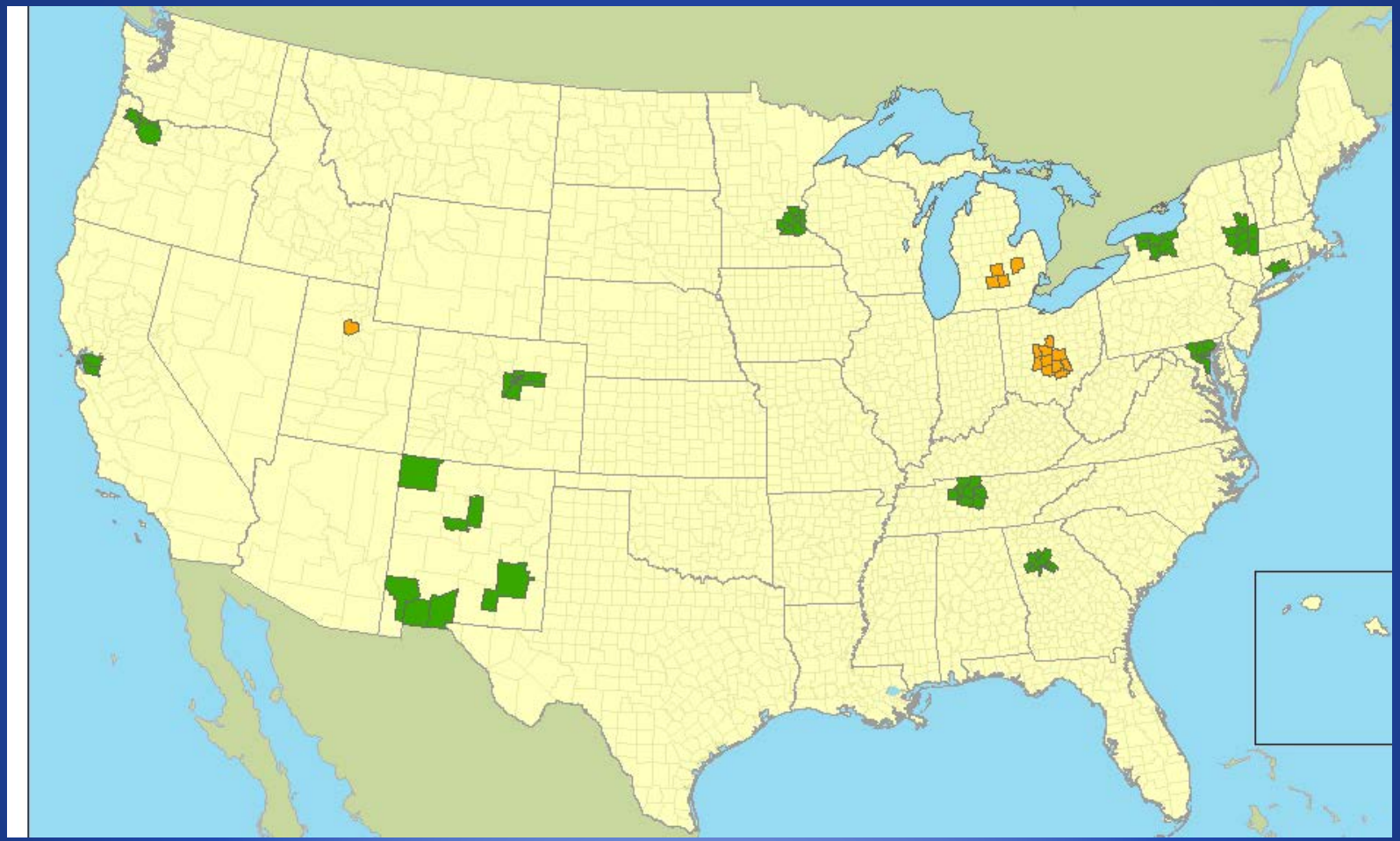


Virometer Data courtesy of Mark Gonzalez and Bob Jerris (CHOA)

FluSurv-NET Laboratory-Confirmed Influenza Hospitalization Surveillance

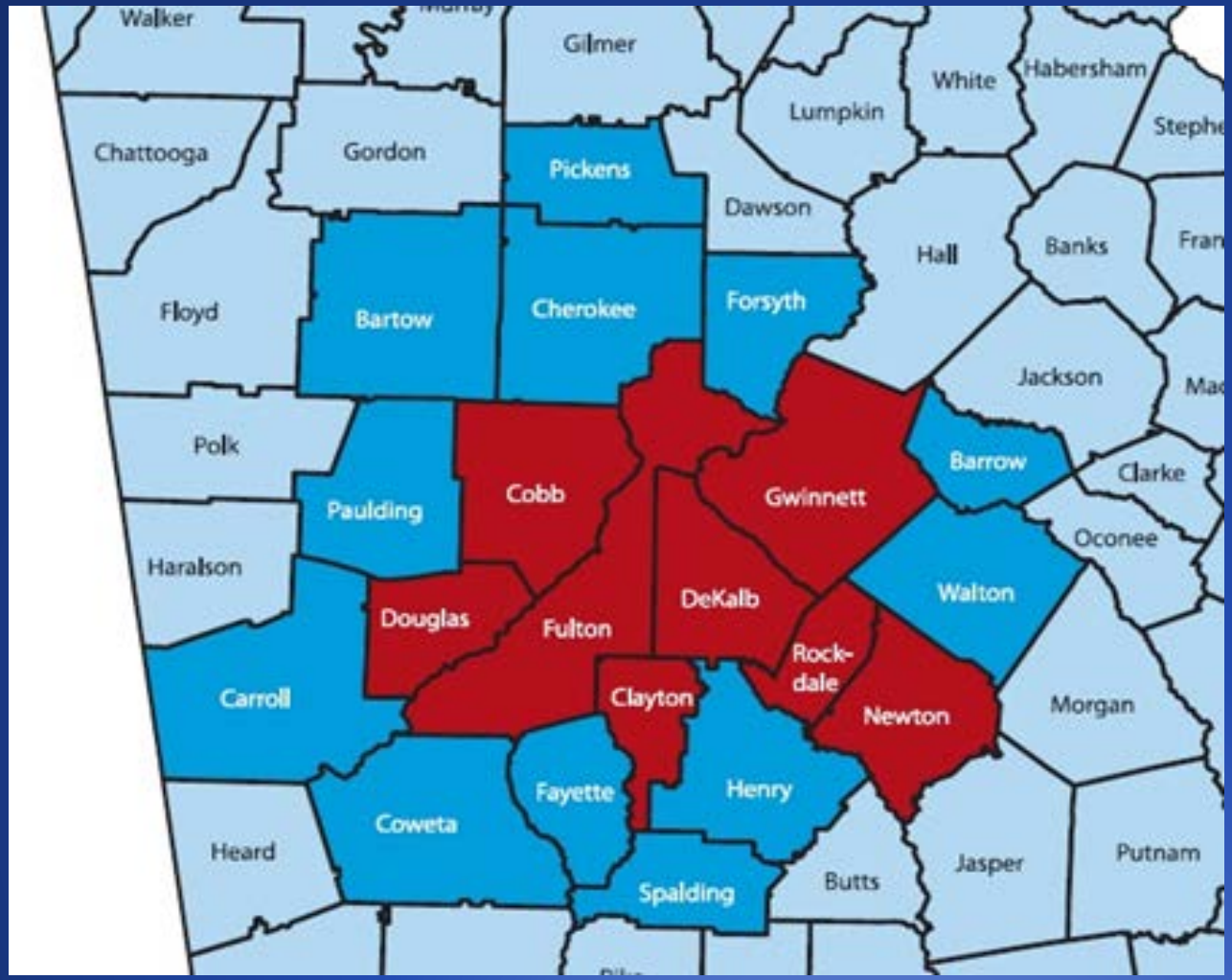


FluSurv-NET Case Definition

- Laboratory test confirmed
- Hospitalized
  - Admitted within 14 days of positive lab test
  - Observation ≥ 24 hours (time spent in ED included)
  - Admitted from October 1-April 30
- Residence and hospitalization in catchment

GEORGIA EIP emerging infections program

FluSurv-NET Catchment-GA



HD3:

- Clayton
- Cobb
- DeKalb
- Douglas
- Fulton
- Gwinnett
- Newton
- Rockdale

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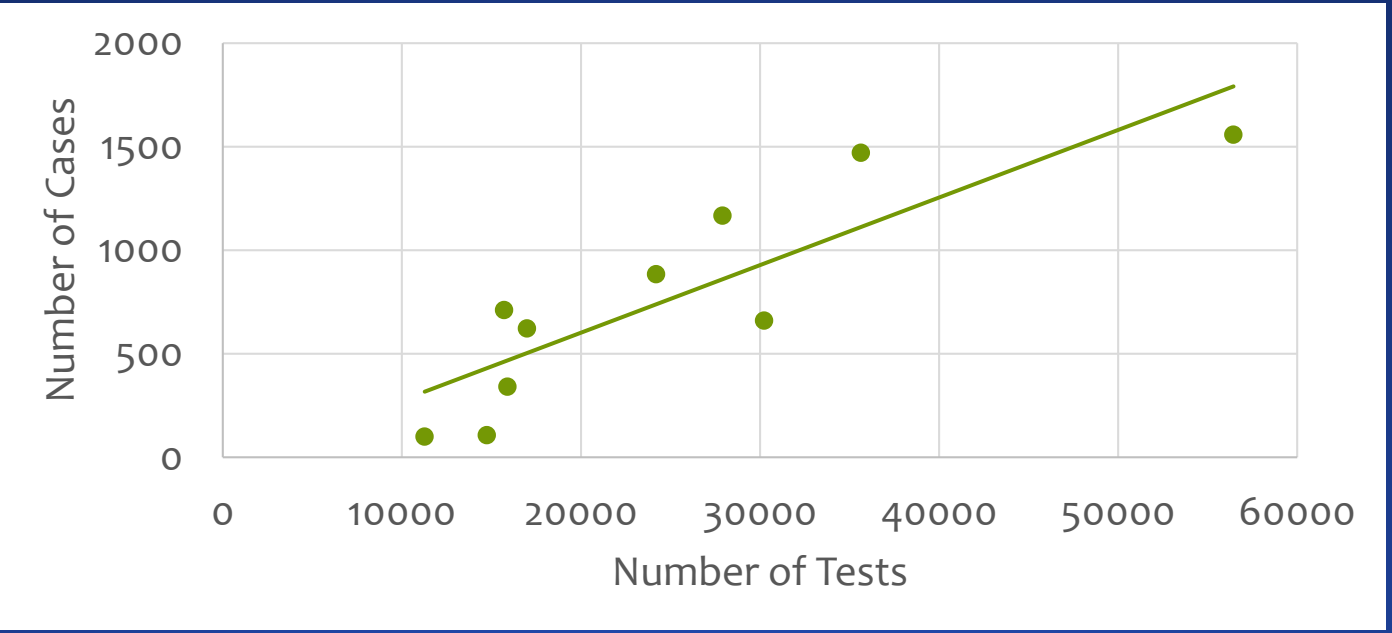
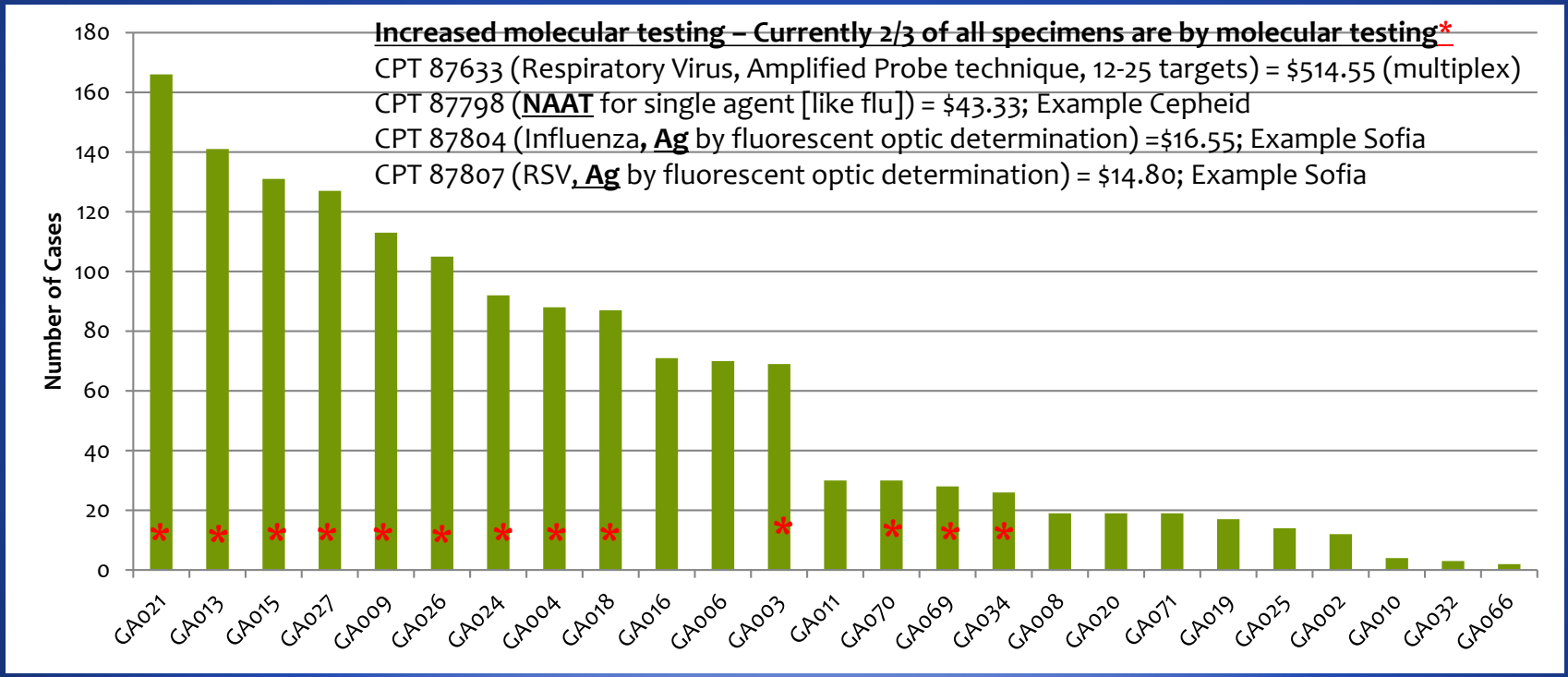
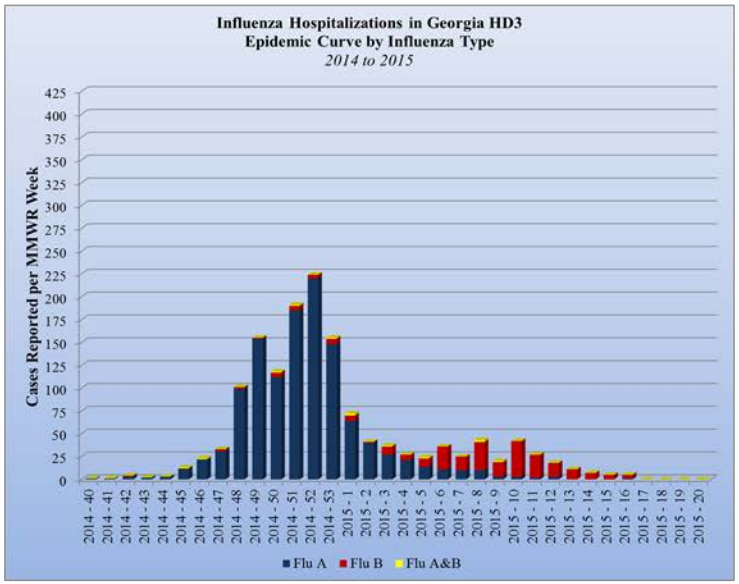
HD3 Hospitalizations

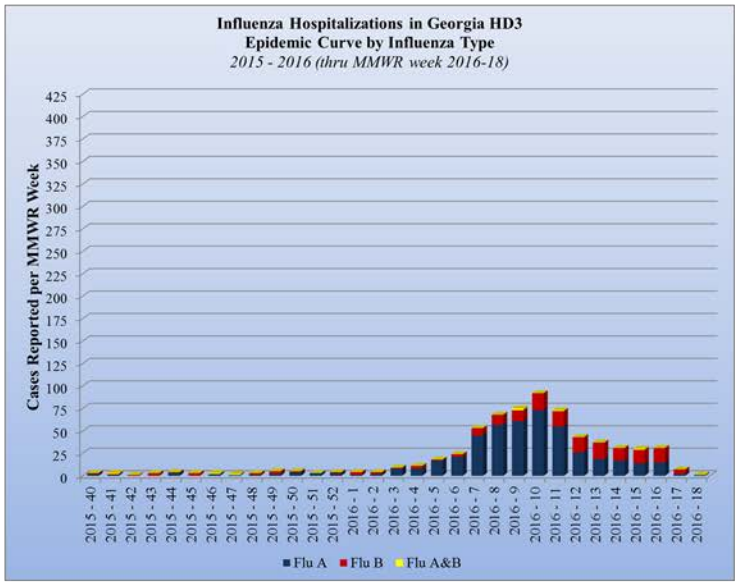
Season	Pediatric	Adult	Total
2003-04	295	---	295
2004-05	76	---	76
2005-06	73	126	199
2006-07	49	80	129
2007-08	71	270	341
2008-09	60	47	107
2009-10 (2009H1N1)	126	585	711
2010-11 (H3N2, B)	125	497	622
2011-12 (H3N2)	12	88	100
2012-13 (H3N2, B)	267	900	1167
2013-14 (2009H1N1)	135	749	884
2014-15 (H3N2, B)	219	1252	1471
2015-16 (2009H1N1)	128	532	660
2016-17 (H3N2, B)	278	1281	1559
2017-18 (H3N2, B)	**353**	**2717**	**3070**

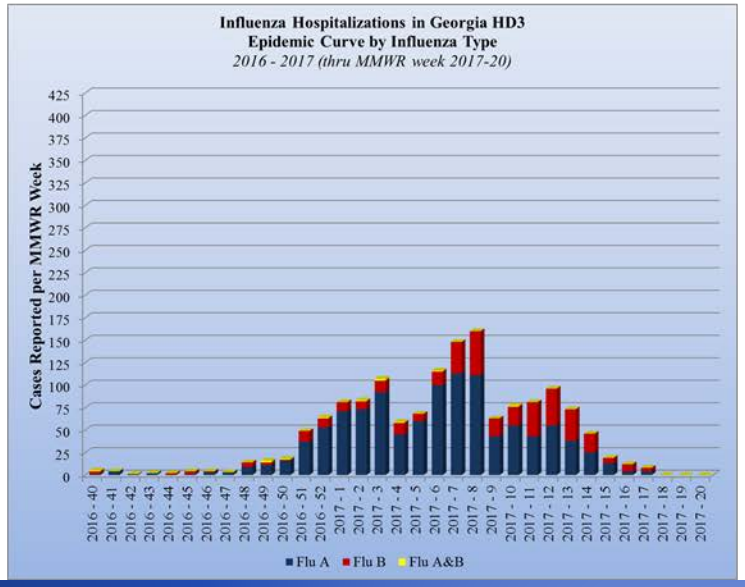

Number of Cases
2000
1500
1000
500
0
0
10000
20000
30000
40000
50000
60000
Number of Tests

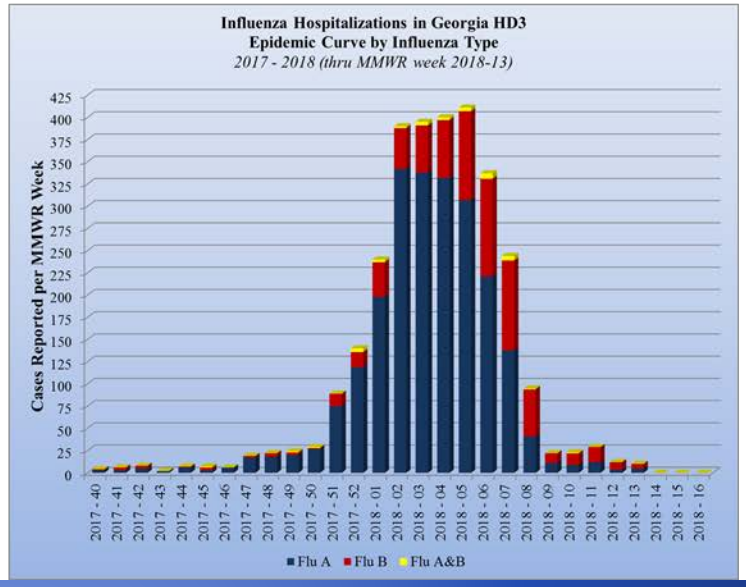

Increased molecular testing – Currently 2/3 of all specimens are by molecular testing*
CPT 87633 (Respiratory Virus, Amplified Probe technique, 12-25 targets) = $514.55 (multiplex)
CPT 87798 (NAAT for single agent [like flu]) = $43.33; Example Cepheid
CPT 87804 (Influenza, Ag by fluorescent optic determination) =$16.55; Example Sofia
CPT 87807 (RSV, Ag by fluorescent optic determination) = $14.80; Example Sofia
Number of Cases
180
160
140
120
100
80
60
40
20
0
GA021
GA013
GA015
GA027
GA009
GA026
GA024
GA004
GA018
GA016
GA006
GA003
GA011
GA070
GA069
GA034
GA008
GA020
GA071
GA019
GA025
GA002
GA010
GA032
GA066

GA Flu Seasons: 2014-15 to 2017-18

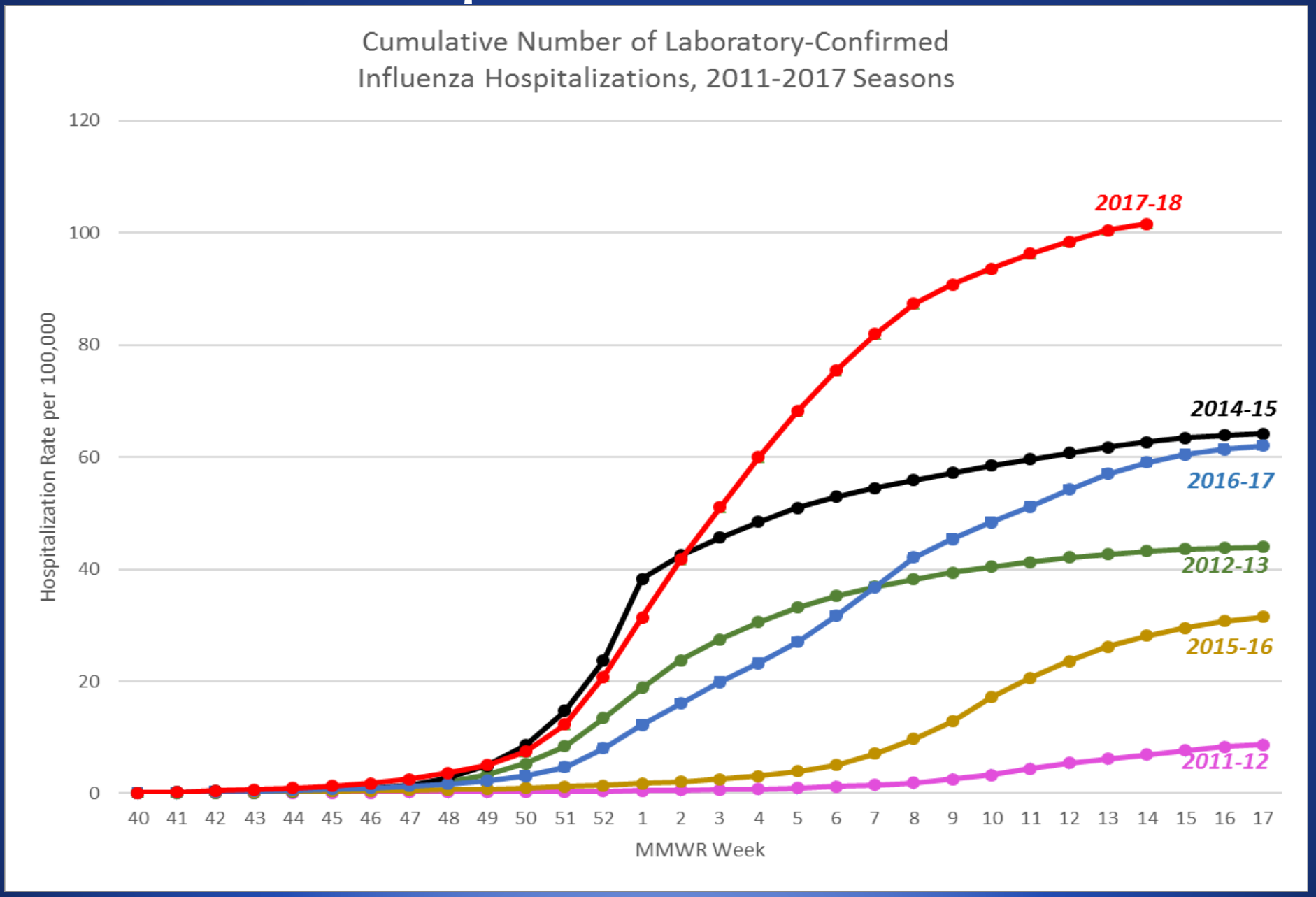








Hospitalization Rates

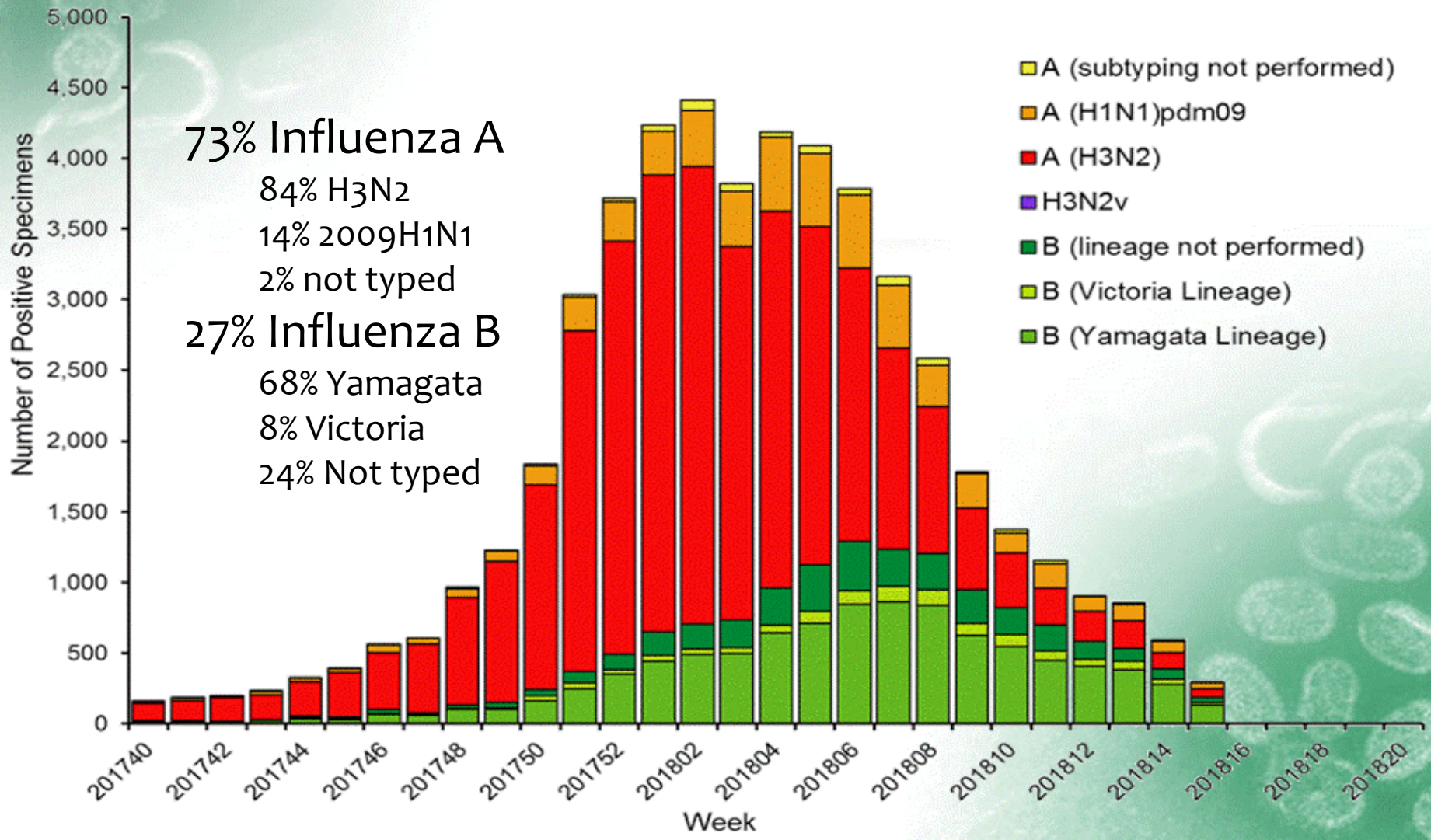


FLUVIEW

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, 2017-2018 Season

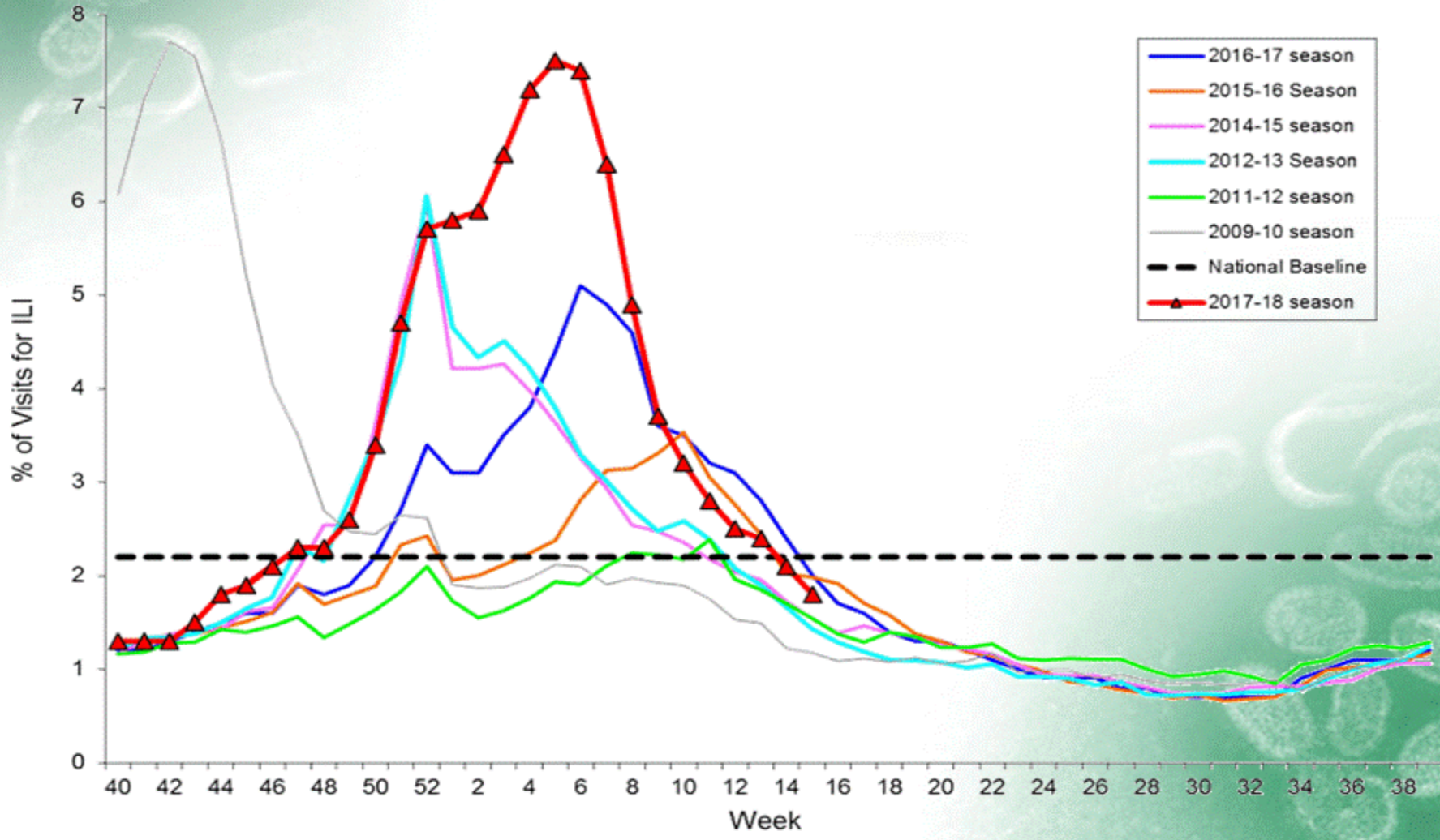


FLUVIEW

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



Why was this influenza season so bad?
PollEverywhere 2 WORD ASSOCIATION

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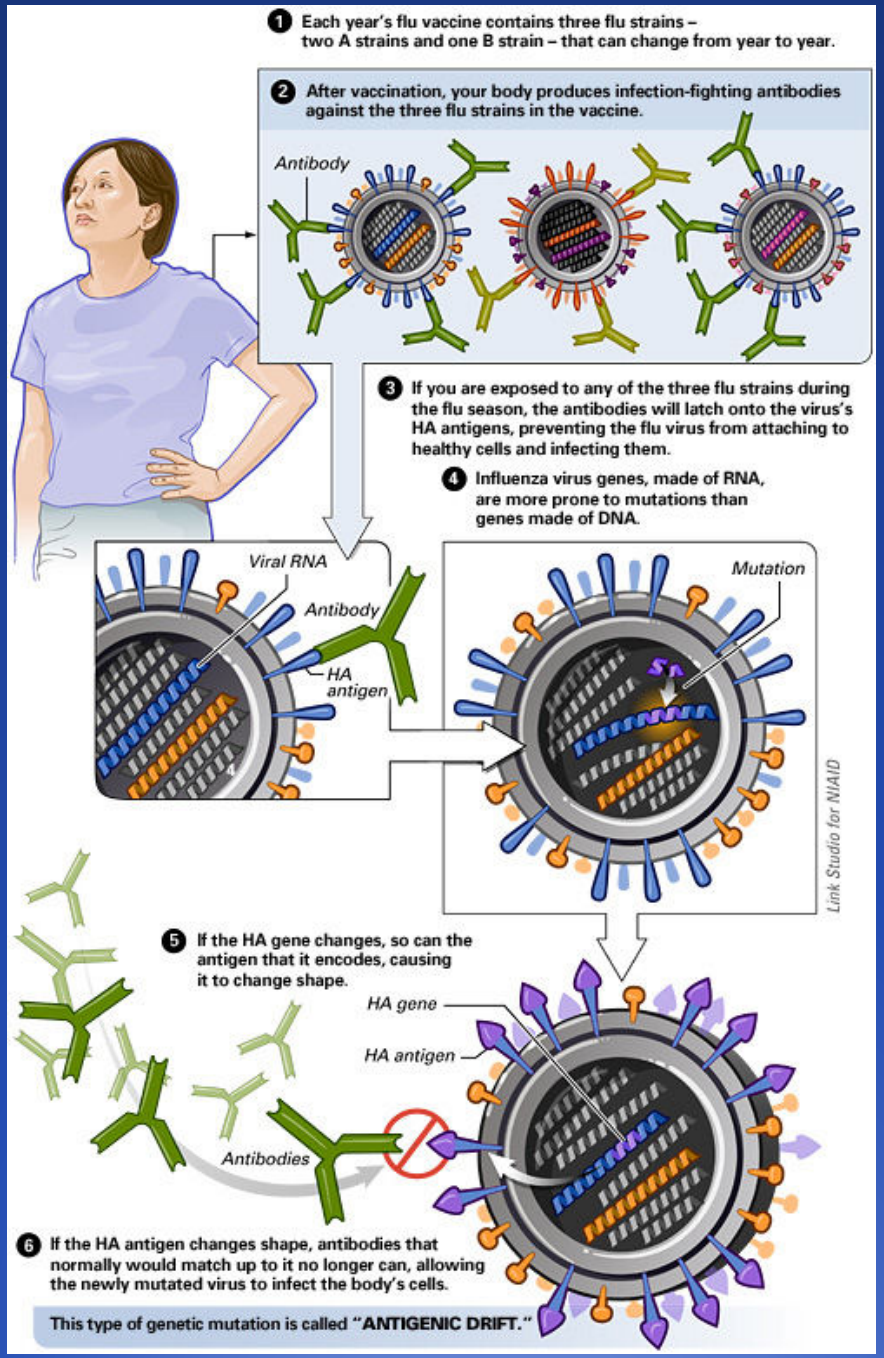
Antigenic Drift



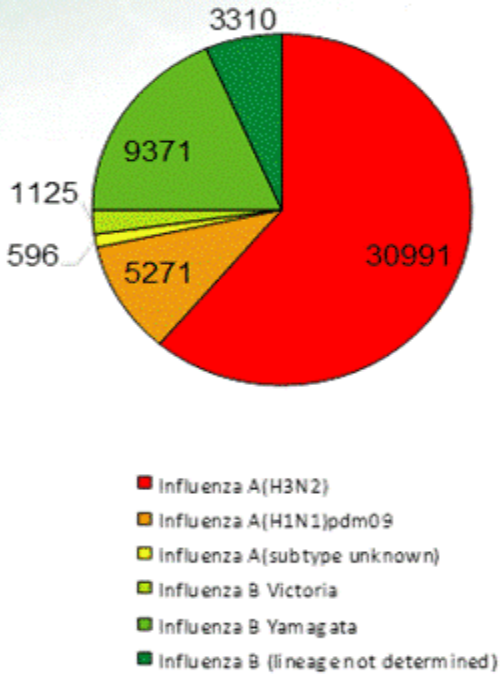
http://www.globalsecurity.org/security/ops/images/antigenic-drift.jpg

FLUVIEW

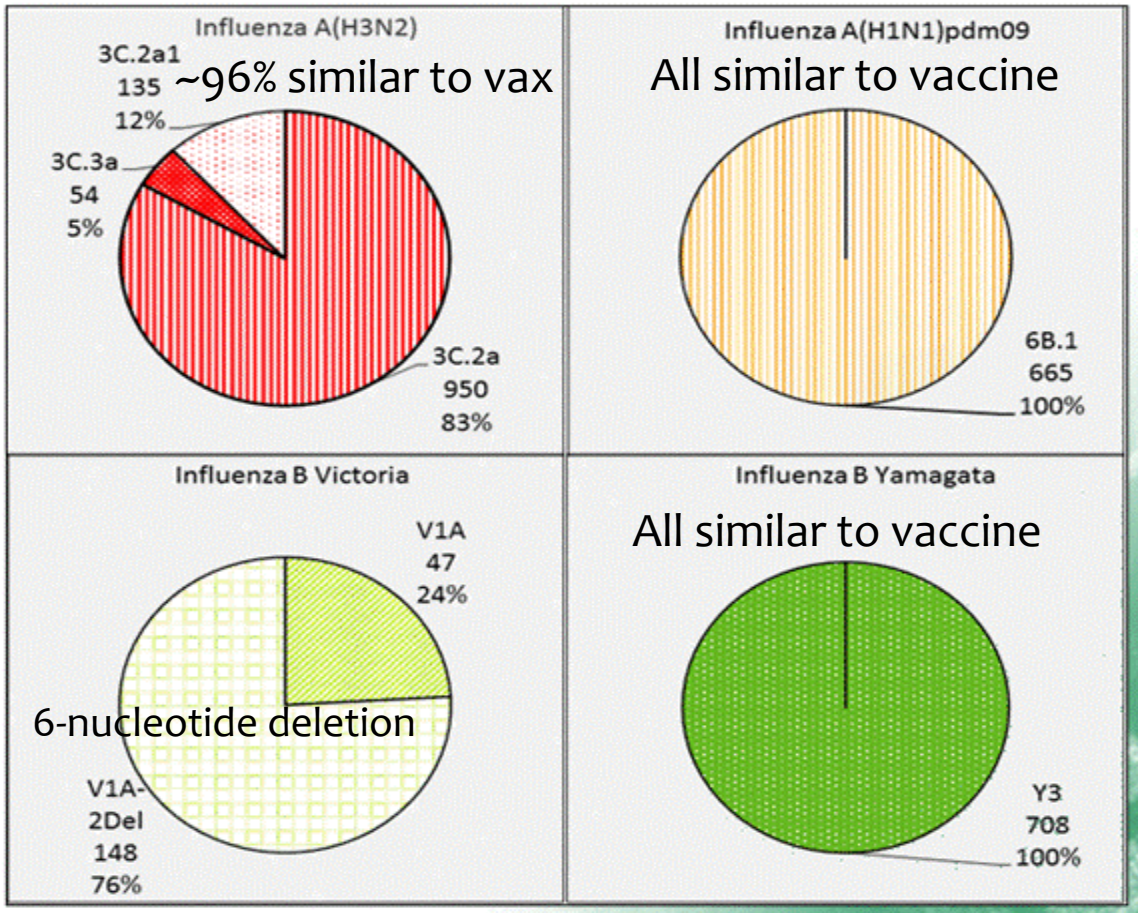
A Weekly Influenza Surveillance Report Prepared by the Influenza Division

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

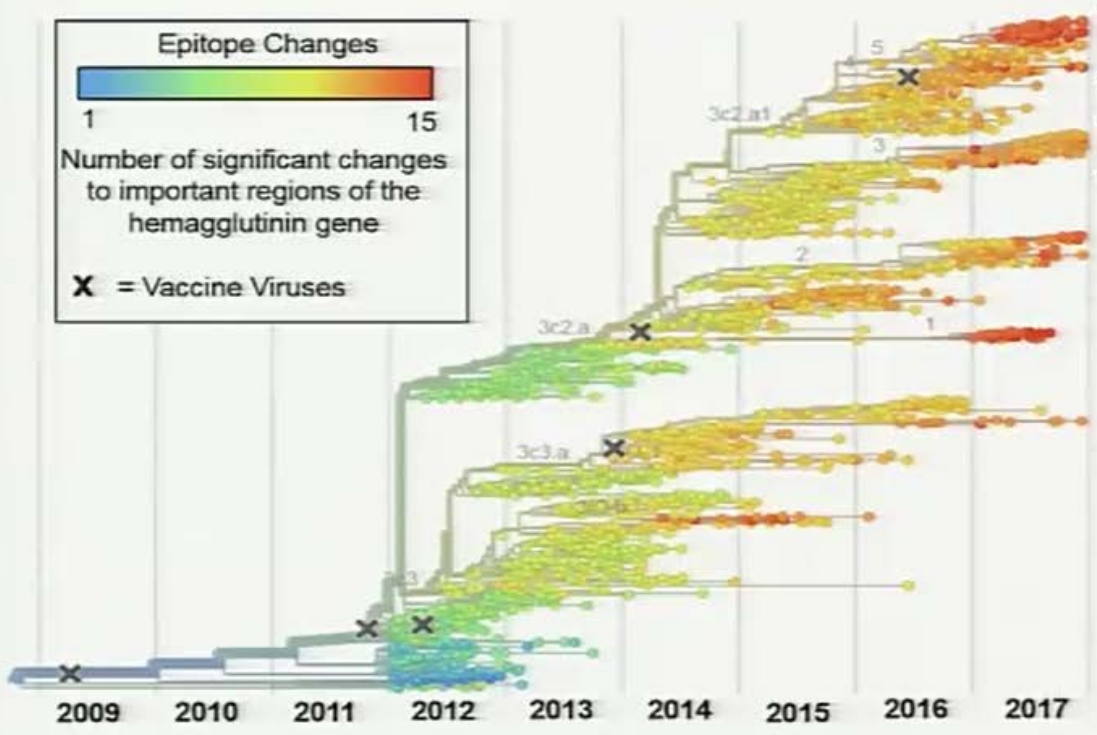
Influenza Positive Specimens Reported by U.S. Public Health Laboratories, Cumulative, 2017-2018 season



Sequence Results, by Genetic HA Clade/Subclade, of Specimens Submitted to CDC by U.S. Public Health Laboratories, Cumulative, 2017-2018 Season



Improved Genetic Characterization Shows Rapid Evolution and Diversity of H3N2



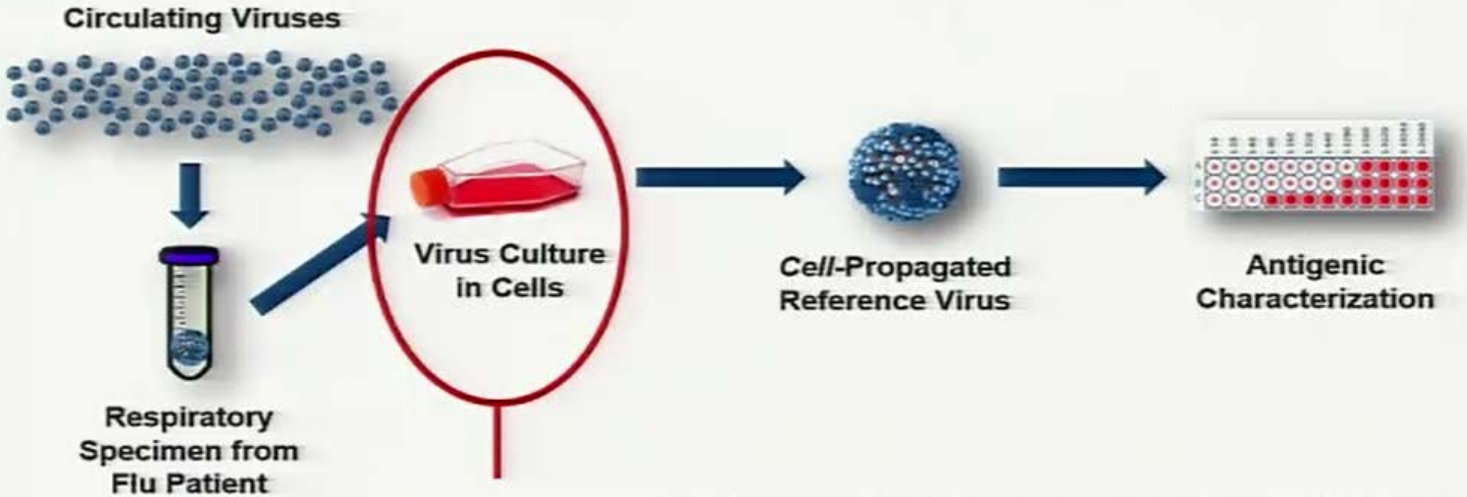
Most common in Australia over summer

Most common in U.S. this season

- Twice the number of vaccine antigen changes that have been made with 2009H1N1
- Increasing divergence

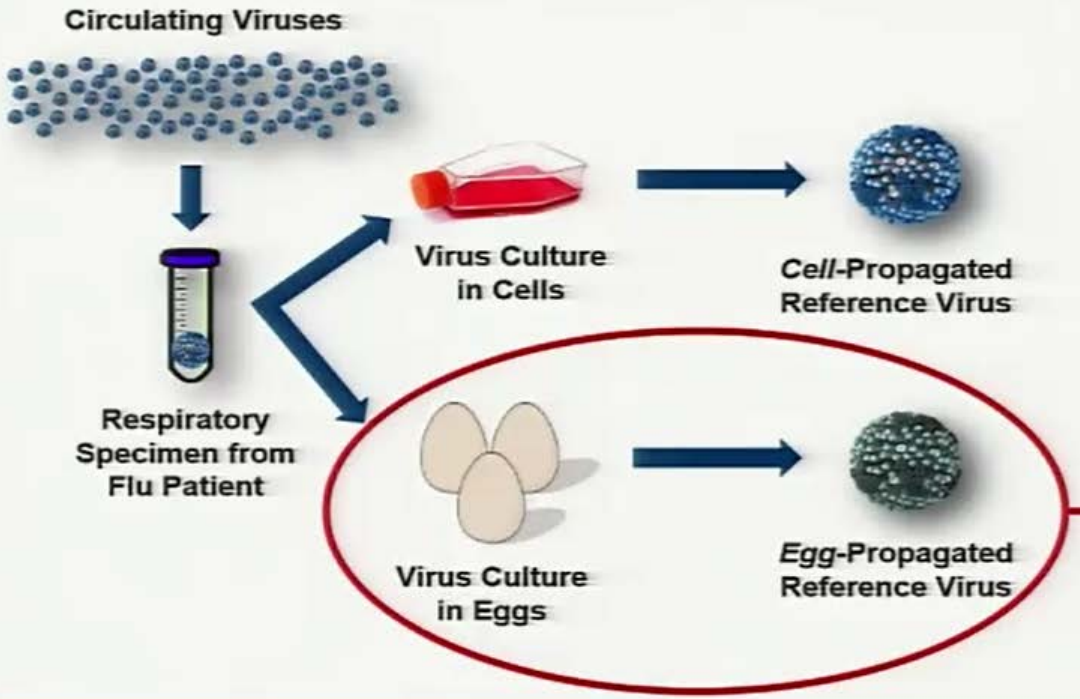
 CDC collaboration with NextFlu. Neher, Bedford et al.

Antigenic Characterization of H3N2 Viruses is Increasingly Difficult



New methods required for propagating H3N2 viruses in cell culture

H3N2 Virus Growth in Eggs Is Increasingly Challenging

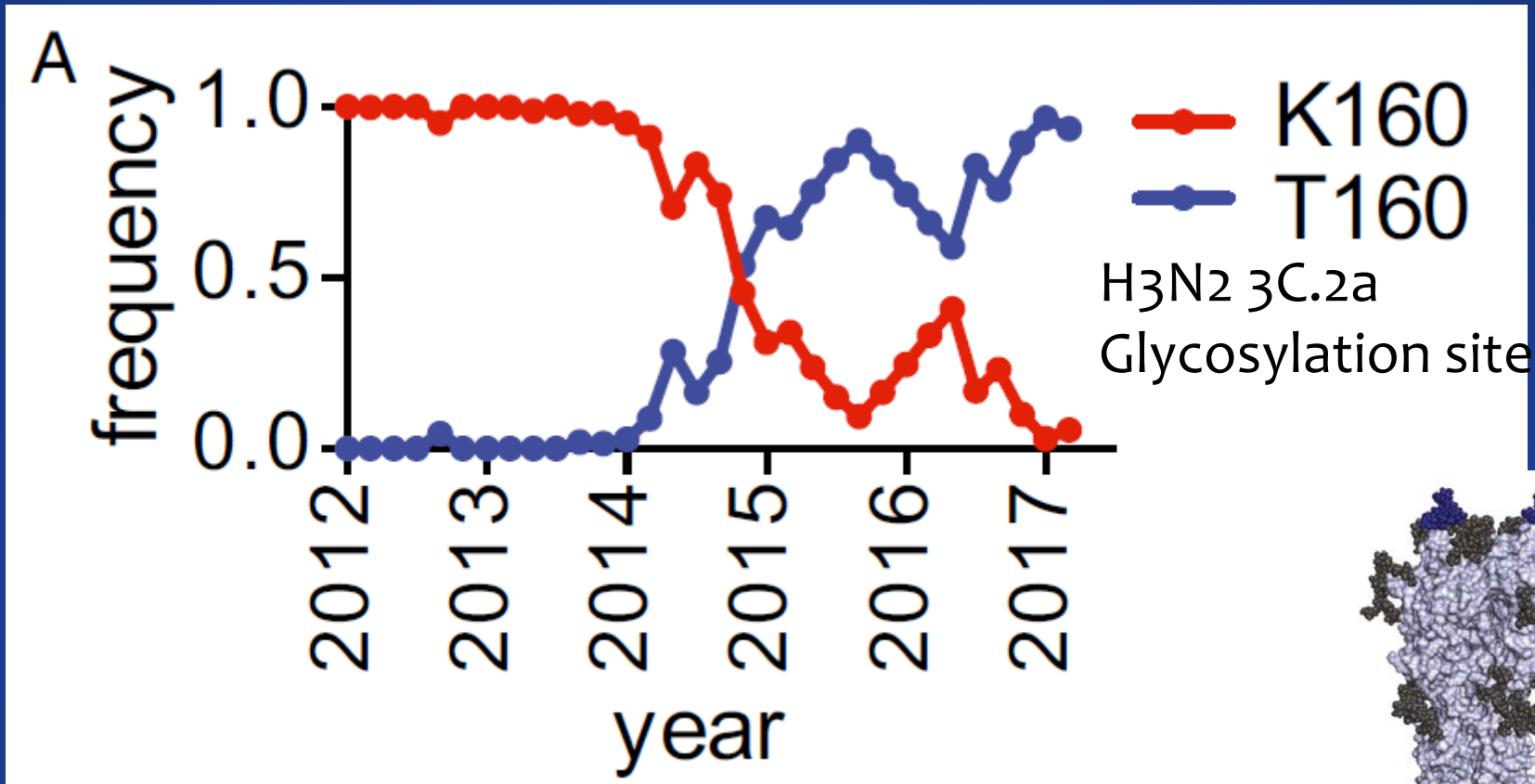


- **Poor Propagation:** H3N2 viruses are difficult to propagate in eggs.
- **Egg Propagation Can Change Antigenicity:** Contemporary H3N2 (3C.2a) viruses acquire changes on the hemagglutinin protein upon propagation in eggs and this can impact the antigenic properties.

Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains

Seth J. Zost[a], Kaela Parkhouse[a], Megan E. Gumina[a], Kangchon Kim[b], Sebastian Diaz Perez[a], Patrick C. Wilson[c], John J. Treanor[d], Andrea J. Sant[e], Sarah Cobey[b], and Scott E. Hensley[a,1]

12578–12583 | PNAS | November 21, 2017 | vol. 114 | no. 47 www.pnas.org/cgi/doi/10.1073/pnas.1712377114



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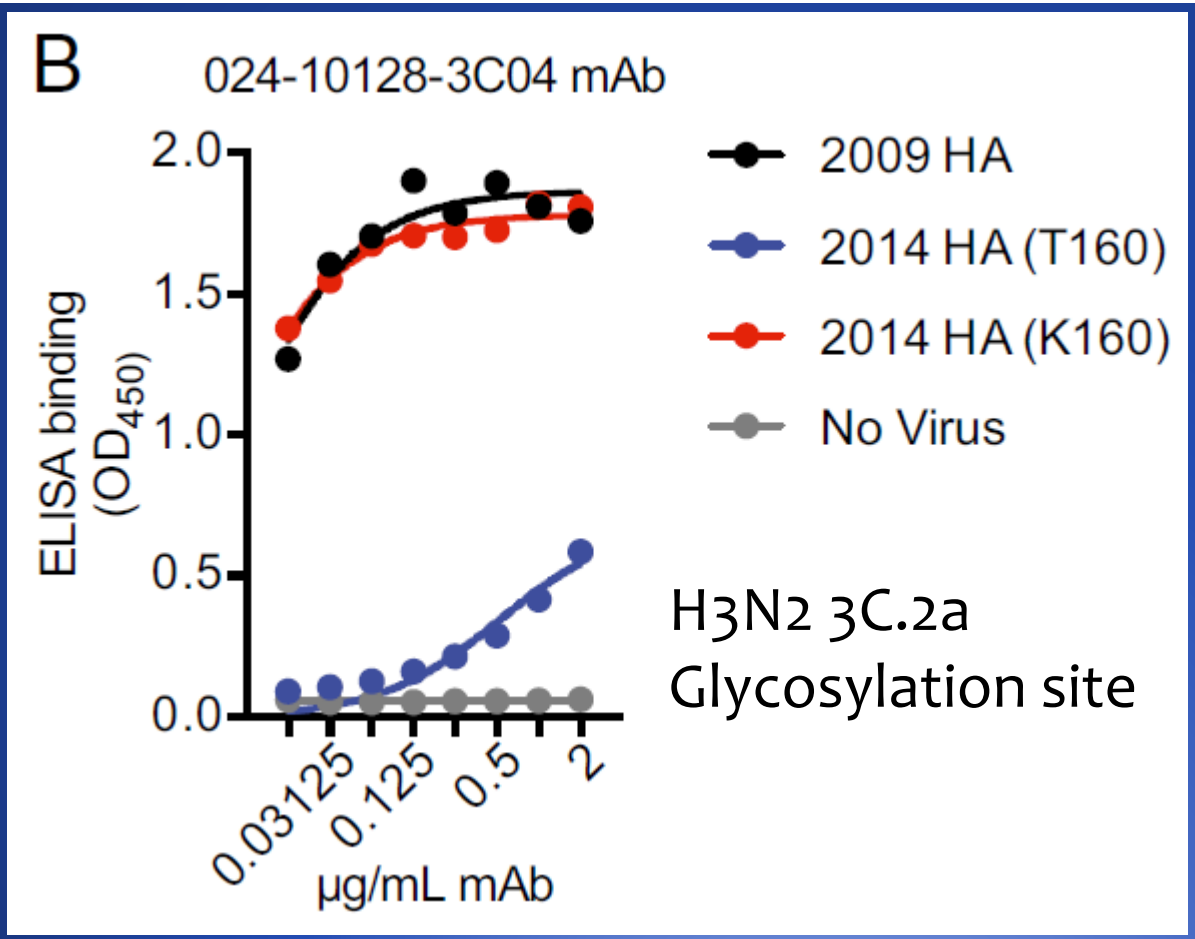

- H3N2 viruses with the K160T HA mutation grow poorly in chicken eggs
- 2016–2017 egg-adapted H3N2 vaccine strain possesses a T160K HA reversion mutation

Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains

Seth J. Zost[a], Kaela Parkhouse[a], Megan E. Gumina[a], Kangchon Kim[b], Sebastian Diaz Perez[a], Patrick C. Wilson[c], John J. Treanor[d], Andrea J. Sant[e], Sarah Cobey[b], and Scott E. Hensley[a,1]

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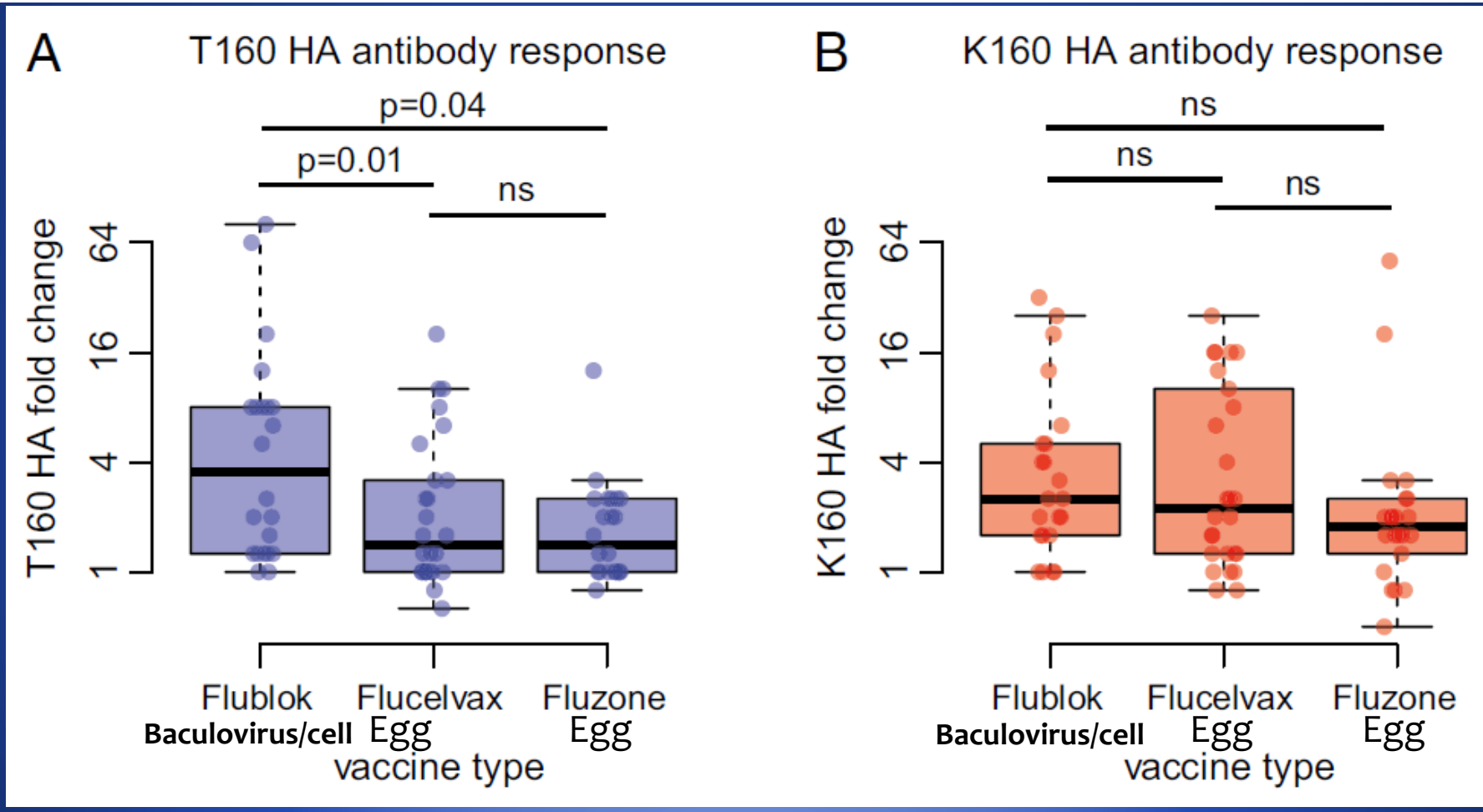


Interim Estimates of 2017–18 Seasonal Influenza Vaccine Effectiveness — United States, February 2018

Brendan Flannery, PhD[1]; Jessie R. Chung, MPH[1]; Edward A. Belongia, MD[2]; Huong Q. McLean, PhD[2]; Manjusha Gaglani, MBBS[3]; Kempapura Murthy, MPH[3]; Richard K. Zimmerman, MD[4]; Mary Patricia Nowalk, PhD[4]; Michael L. Jackson, PhD[5]; Lisa A. Jackson, MD[5]; Arnold S. Monto, MD[6]; Emily T. Martin, PhD[6]; Angie Foust, MS[1]; Wendy Sessions, MPH[1]; LaShondra Berman, MS[1]; John R. Barnes, PhD[1]; Sarah Spencer, PhD[1]; Alicia M. Fry, MD[1]

180 MMWR / February 16, 2018 / Vol. 67 / No. 6 US Department of Health and Human Services/Centers for Disease Control and Prevention

TABLE 2. Number and percentage receiving 2017–18 seasonal influenza vaccine among 4,562 enrolled outpatients with medically attended acute respiratory illness and cough, by influenza test result status, age group, and vaccine effectiveness against all influenza A and B and against virus types A(H3N2), A(H1N1)pdm09 and B — U.S. Influenza Vaccine Effectiveness Network, United States, November 2, 2017–February 3, 2018

	Test result status				Vaccine effectiveness*	
	Influenza-positive		Influenza-negative		Unadjusted	Adjusted
Influenza type/Age group	Total	No. (%) vaccinated	Total	No. (%) vaccinated	% (95% CI)	% (95% CI)
Influenza A and B						
Overall	**1,712**	**741 (43)**	**2,850**	**1,518 (53)**	**33 (24 to 41)**	**36 (27 to 44)†**
Age group (yrs)						
6 mos–8	359	127 (35)	739	408 (55)	56 (42 to 66)	59 (44 to 69)†
9–17	288	100 (35)	300	104 (35)	0 (-41 to 29)	5 (-38 to 34)
18–49	561	198 (35)	989	444 (45)	33 (17 to 46)	33 (16 to 47)†
50–64	288	159 (55)	454	277 (61)	21 (-6 to 42)	17 (-15 to 40)
≥65	216	157 (73)	368	285 (78)	23 (-14 to 47)	18 (-25 to 47)
Influenza A(H3N2)						
Overall	**1,143**	**530 (46)**	**2,850**	**1,518 (53)**	**24 (13 to 34)**	**25 (13 to 36)†**
Age group (yrs)						
6 mos–8	200	79 (40)	739	408 (55)	47 (27 to 61)	51 (29 to 66)†
9–17	203	75 (37)	300	104 (35)	-10 (-60 to 24)	-8 (-62 to 29)
18–49	395	155 (39)	989	444 (45)	21 (-1 to 37)	20 (-4 to 38)
50–64	198	115 (58)	454	277 (61)	11 (-24 to 37)	12 (-26 to 39)
≥65	147	106 (72)	368	285 (78)	25 (-16 to 51)	17 (-35 to 49)
Influenza A(H1N1)pdm09						
Overall	**208**	**60 (29)**	**2,850**	**1,518 (53)**	**64 (52 to 74)**	**67 (54 to 76)†**
Age group (yrs)						
<18	105	22 (21)	1,039	512 (49)	73 (56 to 83)	78 (63 to 87)†
18–64	84	26 (31)	1,443	721 (50)	55 (28 to 72)	51 (20 to 70)†
≥65	19	12 (63)	368	285 (78)	50 (-31 to 81)	34 (-96 to 78)
Influenza B						
Overall	**323**	**132 (41)**	**2,850**	**1,518 (53)**	**39 (23 to 52)**	**42 (25 to 56)†**
Age group (yrs)						
<18	127	46 (36)	1,039	512 (49)	42 (14 to 60)	36 (1 to 58)†
18–64	151	53 (35)	1,443	721 (50)	46 (23 to 62)	50 (28 to 66)†
≥65	45	33 (73)	368	285 (78)	20 (-62 to 60)	25 (-62 to 66)

Abbreviation: CI = confidence interval.

* Vaccine effectiveness was estimated as 100% x (1 - odds ratio [ratio of odds of being vaccinated among outpatients with influenza-positive test results to the odds of being vaccinated among outpatients with influenza-negative test results]); odds ratios were estimated using logistic regression.

† Statistically significant at the $p<0.05$ level.

Why was this influenza season so bad?

You were correct! (We don’t know)

GA EIP Influenza Case Rates by Age Category, 2016-17

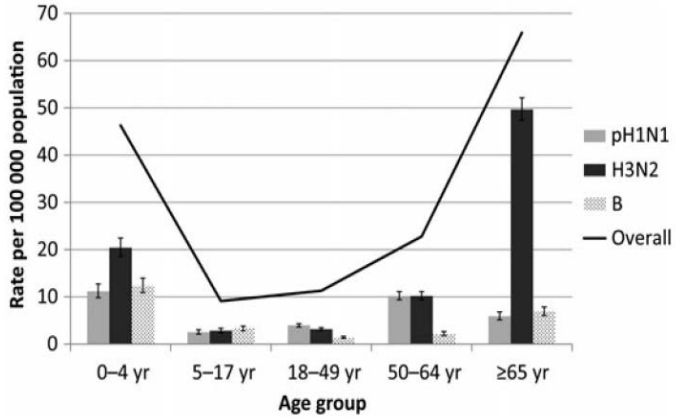


Figure 1. Laboratory-confirmed influenza hospitalization rates by virus type and subtype and age group, United States, 2010–2011 influenza season.

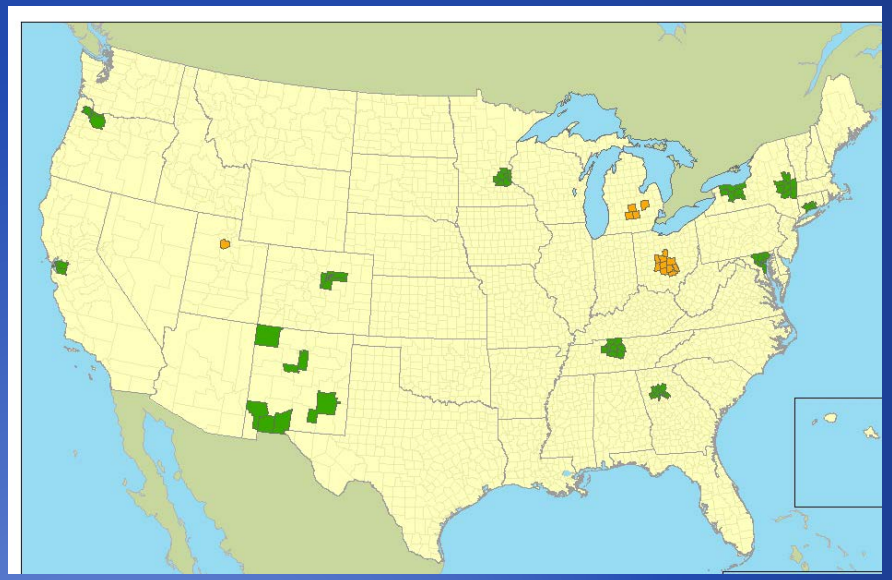
The Journal of Infectious Diseases 2013;208:1305–14

Influenza Vaccine Updates

How well do we do at influenza vaccination in the state of Georgia?

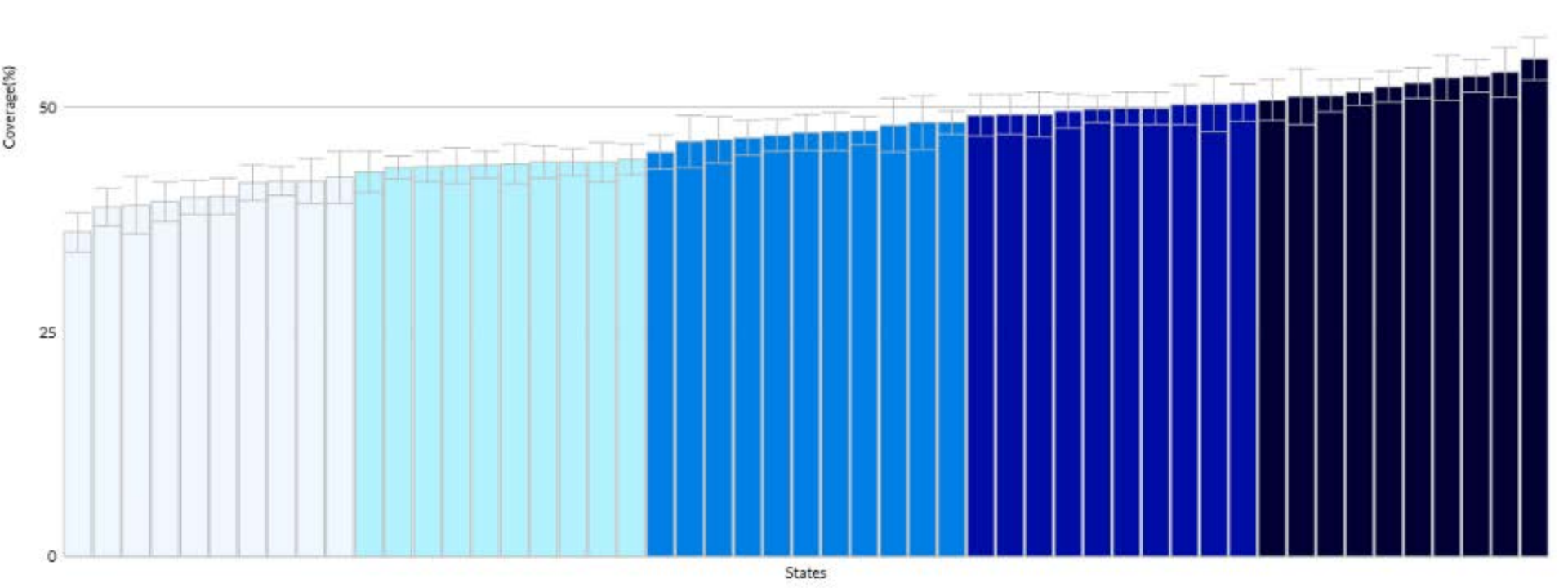
PollEverywhere

- A) #1
- B) #13
- C) #26
- D) #39
- E) #52



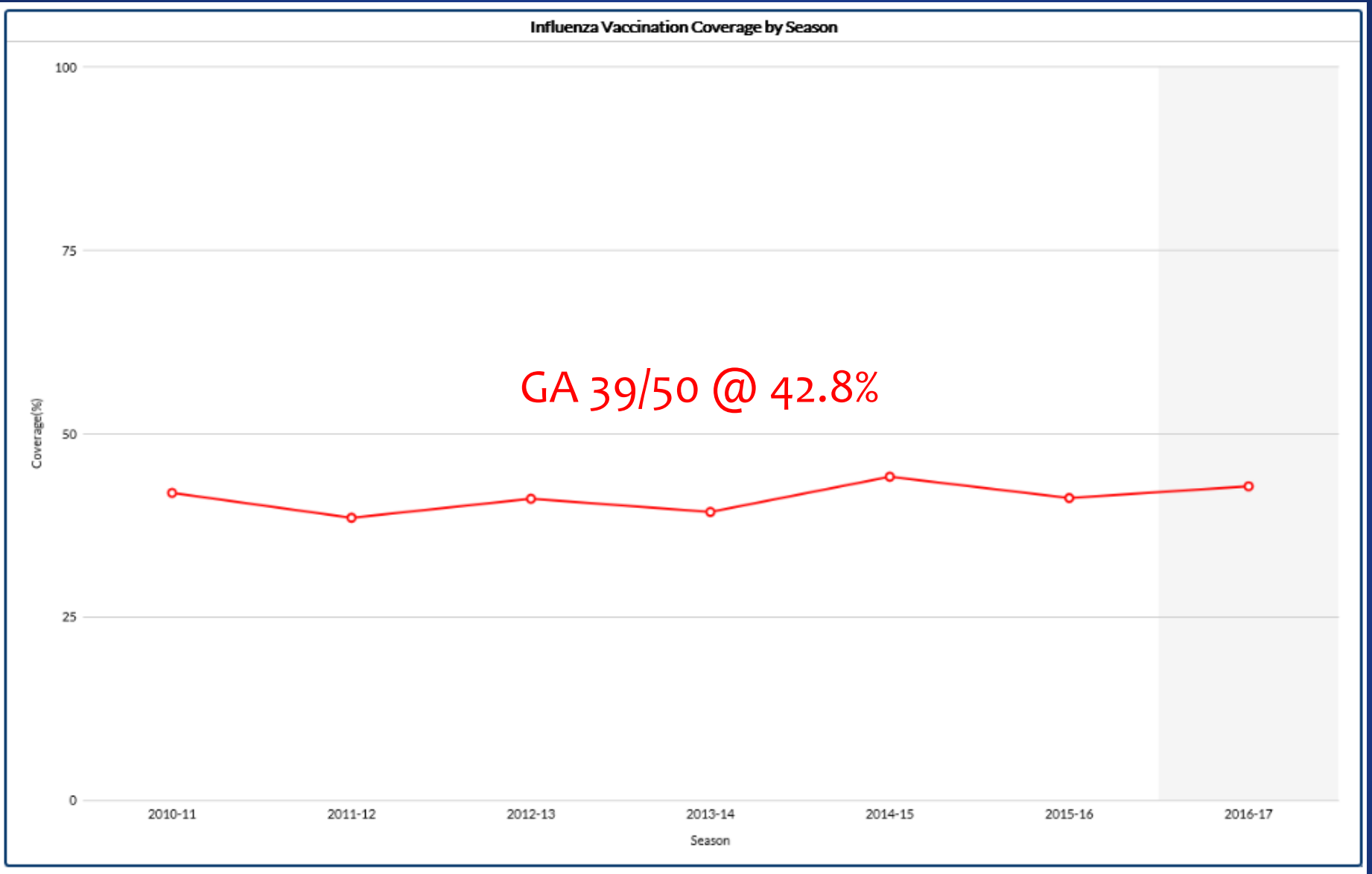
Influenza Vaccination – National Health Interview Survey

GA 39/50 @ 42.8%



https://www.cdc.gov/flu/fluvaxview/reportshtml/reporti1617/reporti/index.html

Influenza Vaccination



https://www.cdc.gov/flu/fluvaxview/reportshtml/reporti1617/reporti/index.html

- *Routine annual influenza vaccination is recommended for all persons age ≥6 months without contraindications.*

TABLE 2. Contraindications and precautions to the use of influenza vaccines — United States, 2017–18 influenza season*

Vaccine type	Contraindications	Precautions
IIV	History of severe allergic reaction to any component of the vaccine† or after previous dose of any influenza vaccine	Moderate-to-severe acute illness with or without fever History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine

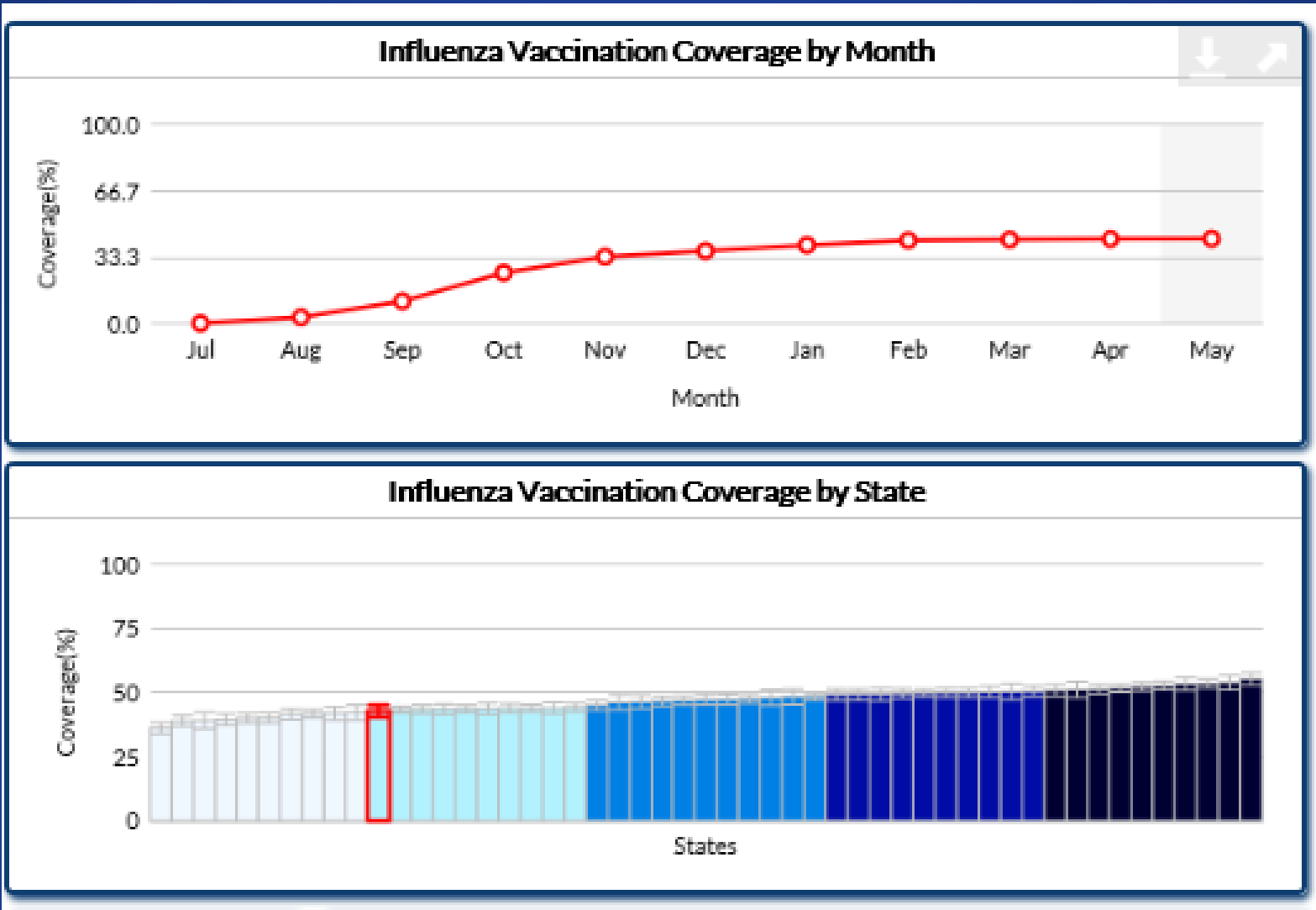
- For the 2018-2019 influenza season, immunization providers are recommended to administer any licensed, age-appropriate influenza vaccine (IIV, RIV, or LAIV). LAIV4 is an option for influenza vaccination for persons for whom it is otherwise appropriate.
- *Influenza vaccine strains:*

2017 – 2018	2018 – 2019
A/Michigan/45/2015 (H1N1) pdm09	*A/Michigan/45/2015 (H1N1) pdm09*
A/Hong Kong/4801/2014 (H3N2)	A/Singapore/INFIMH-16-0019/2016 (H3N2)
B/Brisbane/60/2008 (B/Victoria)	B/Colorado/06/2017 (B/Victoria)
Quad: *B/Phuket/3073/2013 (B/Yamagata)*	Quad: *B/Phuket/3073/2013 (B/Yamagata)*

TABLE 1. Influenza vaccines — United States, 2017–18 influenza season*

Trade name	Manufacturer	Presentation	Age indication	Mercury (from thimerosal, µg/0.5 mL)	Latex	Route
Inactivated influenza vaccines, quadrivalent (IIV4s), standard-dose†						
Afluria Quadrivalent	Seqirus	0.5 mL prefilled syringe	≥18 years	NR	No	IM§
		5.0 mL multidose vial	≥18 years (by needle/syringe) 18 through 64 years (by jet injector)	24.5	No	IM
Fluarix Quadrivalent	GlaxoSmithKline	0.5 mL prefilled syringe	≥3 years	NR	No	IM
FluLaval Quadrivalent	ID Biomedical Corp. of Quebec (distributed by GlaxoSmithKline)	0.5 mL prefilled syringe	≥6 months	NR	No	IM
		5.0 mL multidose vial	≥6 months	<25	No	IM
Fluzone Quadrivalent	Sanofi Pasteur	0.25 mL prefilled syringe	6 through 35 months	NR	No	IM
		0.5 mL prefilled syringe	≥3 years	NR	No	IM
		0.5 mL single-dose vial	≥3 years	NR	No	IM
		5.0 mL multidose vial	≥6 months	25	No	IM
Inactivated influenza vaccine, quadrivalent (ccIIV4), standard-dose,† cell culture-based						
Flucelvax Quadrivalent	Seqirus	0.5 mL prefilled syringe	≥4 years	NR	No	IM
		5.0 mL multidose vial	≥4 years	25	No	IM
Inactivated influenza vaccine, quadrivalent (IIV4), standard-dose, intradermal¶						
Fluzone Intradermal Quadrivalent	Sanofi Pasteur	0.1 mL single-dose prefilled microinjection system	18 through 64 years	NR	No	ID**
Inactivated Influenza Vaccines, trivalent (IIV3s), standard-dose†						
Afluria	Seqirus	0.5 mL prefilled syringe	≥5 years	NR	No	IM
		5.0 mL multidose vial	≥5 years (by needle/syringe) 18 through 64 years (by jet injector)	24.5	No	IM
Fluvirin	Seqirus	0.5 mL prefilled syringe	≥4 years	≤1	Yes††	IM
		5.0 mL multidose vial	≥4 years	25	No	IM
Adjuvanted inactivated influenza vaccine, trivalent (aIIV3),† standard-dose						
Fluad	Seqirus	0.5 mL prefilled syringe	≥65 years	NR	Yes††	IM
Inactivated Influenza Vaccine, trivalent (IIV3), high-dose§§						
Fluzone High-Dose	Sanofi Pasteur	0.5 mL prefilled syringe	≥65 years	NR	No	IM
Recombinant Influenza Vaccine, quadrivalent (RIV4)¶¶						
Flublok Quadrivalent	Protein Sciences	0.5 mL prefilled syringe	≥18 years	NR	No	IM
Recombinant Influenza Vaccine, trivalent (RIV3)¶¶						
Flublok	Protein Sciences	0.5 mL single-dose vial	≥18 years	NR	No	IM
Live Attenuated Influenza Vaccine, quadrivalent (LAIV4)* (not recommended for use during the 2017–18 season)**						
FluMist Quadrivalent	MedImmune	0.2 mL single-dose prefilled intranasal sprayer	2 through 49 years	NR	No	NAS

Does seasonal influenza vaccine effectiveness decrease over the season (time dependent)?



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Intraseason Waning of Influenza Vaccine Protection: Evidence From the US Influenza Vaccine Effectiveness Network, 2011–2012 Through 2014–2015

Jill M. Ferdinands,[1] Alicia M. Fry,[1] Sue Reynolds,[1,2] Joshua G. Petrie,[3] Brendan Flannery,[1] Michael L. Jackson,[4] and Edward A. Belongia[5]

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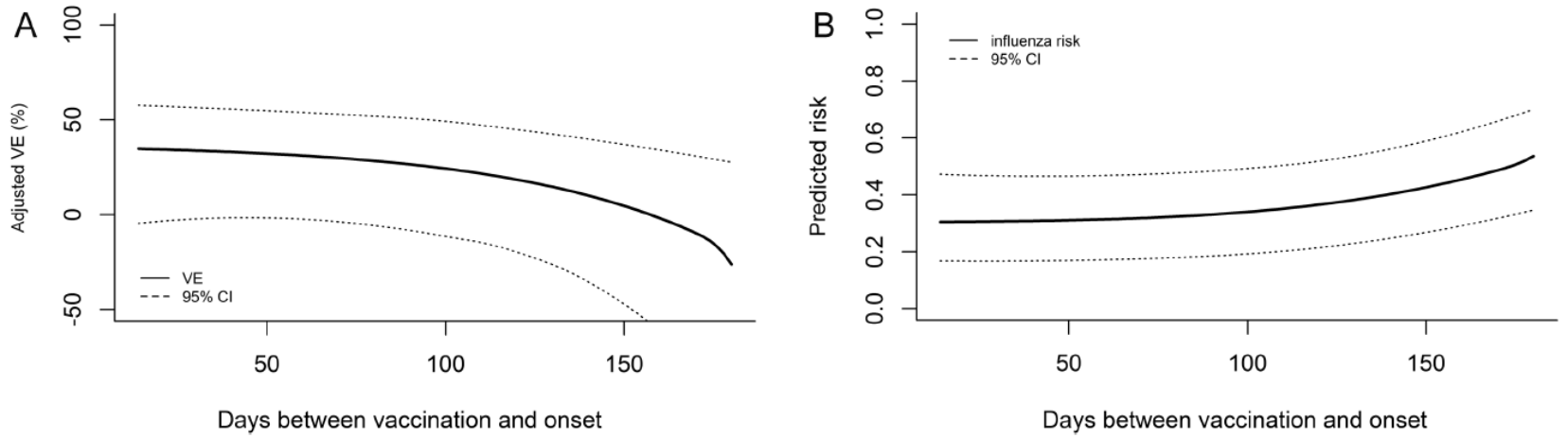

Figure 2. US Influenza Vaccine Effectiveness Network, 2011–2012 through 2014–2015. *A*, Adjusted vaccine effectiveness (VE) against influenza A(H3N2) virus infection by days since vaccination. Maximum VE was 35% at 14 days postvaccination. VE reached zero at 158 days postvaccination. Adjusted VE without including time since vaccination in the model was 24% (95% CI, 15%–32%). *B*, Predicted risk of influenza A(H3N2) virus infection by days since vaccination in dataset limited to vaccinees. Abbreviations: CI, confidence interval, VE, vaccine effectiveness

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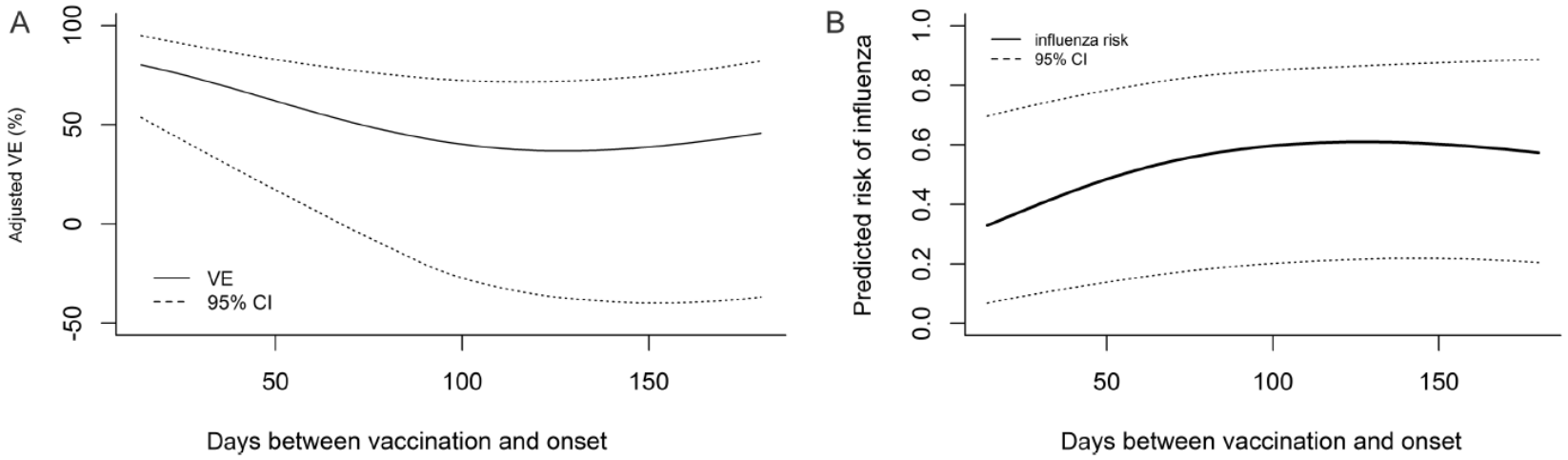

Figure 3. US Influenza Vaccine Effectiveness Network, 2011–2012 through 2013–2014. *A*, Adjusted vaccine effectiveness (VE) against influenza A(H1N1)pdm09 virus infection by days since vaccination. Maximum VE was 80% at 14 days postvaccination and minimum VE was 37% at 128 days postvaccination. VE was 46% at 180 days postvaccination. Adjusted VE without including time since vaccination in the model was 48% (95% confidence interval [CI], 36%–58%). *B*, Predicted risk of influenza A(H1N1) pdm09 virus infection by days since vaccination in dataset limited to vaccinees.

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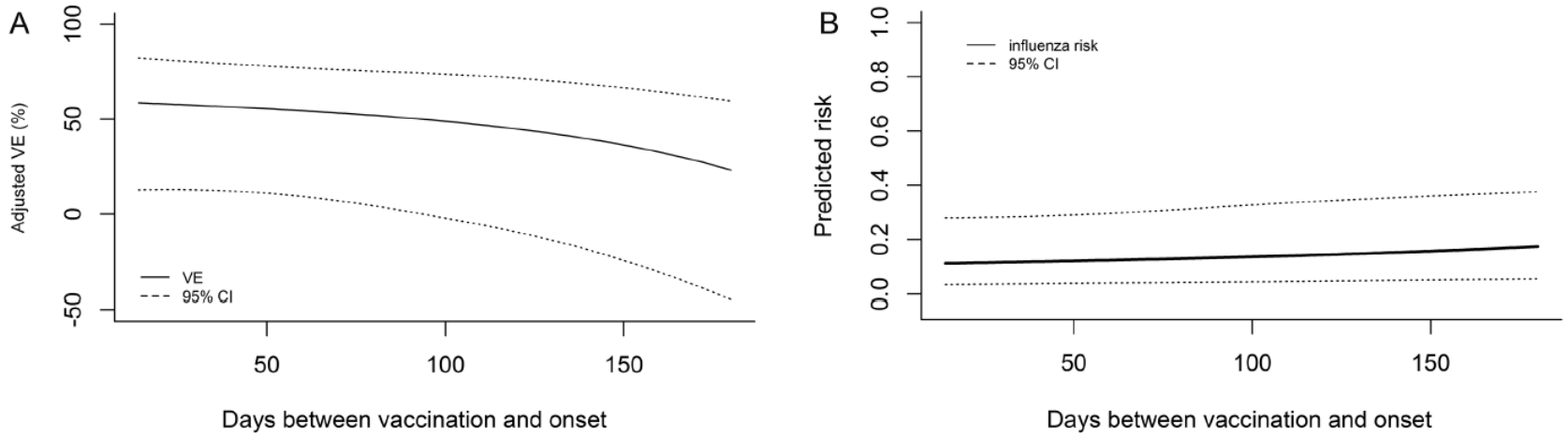

Figure 4. US Influenza Vaccine Effectiveness Network, 2011–2012 through 2014–2015. *A*, Adjusted vaccine effectiveness (VE) against influenza B virus infection by days since vaccination. Maximum vaccine effectiveness (VE) was 59% at 14 days postvaccination and minimum VE was 23% at 180 days postvaccination. Adjusted VE without including time since vaccination in the model was 45% (95% confidence interval [CI], 33%–54%). *B*, Predicted risk of influenza B virus infection by days since vaccination in dataset limited to vaccinees.

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What is this vaccine's effectiveness?

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Walt Orenstein: Vaccinations save lives

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Conclusion: The possibility of waning VE merits further investigation; however, the current uncertainty in its nature and magnitude makes drawing conclusions difficult and suggests the careful consideration of the risks and benefits of delaying vaccination is needed before contemplating changes to current vaccine recommendations.

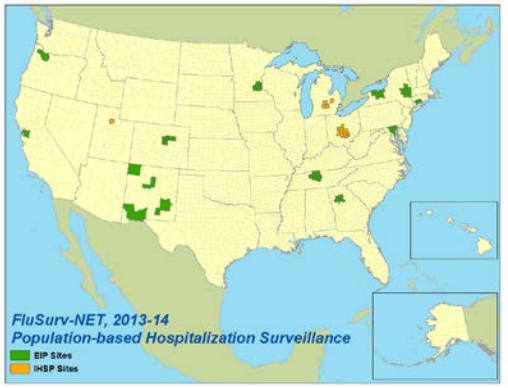
In the setting of an influenza vaccine failure, does influenza vaccine still modify the severity of influenza illness?

Does Influenza Vaccination Modify Influenza Severity? Data on Older Adults Hospitalized With Influenza During the 2012–2013 Season in the United States

H3N2 predominant

The Journal of Infectious Diseases® 2015;212:1200–8

Carmen S. Arriola,[1,2] Evan J. Anderson,[3,4] Joan Baumbach,[5] Nancy Bennett,[6] Susan Bohm,[8] Mary Hill,[9] Mary Lou Lindegren,[10] Krista Lung,[11] James Meek,[12] Elizabeth Mermel,[13] Lisa Miller,[14] Maya L. Monroe,[15] Craig Morin,[16] Oluwakemi Oni,[17] Arthur Reingold,[18] William Schaffner,[10] Ann Thomas,[19] Shelley M. Zansky,[7] Lyn Finelli,[2] and Sandra S. Chaves[2]



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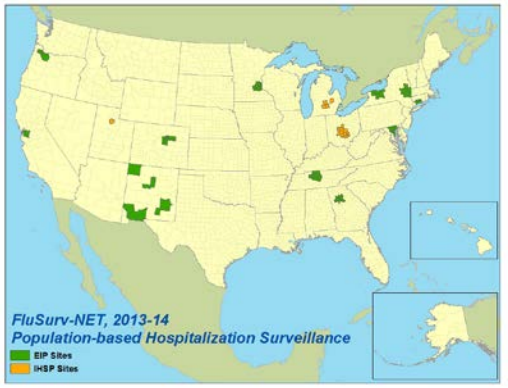

Table 3. Influenza Vaccination and Severity of Influenza Analysis for 1509 Cases Treated With Antivirals During the 2012–2013 Influenza Season, by Age Group, After Propensity Score Matching

	50–64 y (n = 494)		65–74 y (n = 495)		≥75 y (n = 520)	
Clinical Outcome	Point Estimate (95% CI)	*P* Value	Point Estimate (95% CI)	*P* Value	Point Estimate (95% CI)	*P* Value
Severe disease, OR[a]	0.97 (.62–1.52)	.89	1.27 (.81–1.99)	.29	0.99[b] (.59–1.66)	.97
Diagnosis of pneumonia, OR[c]	0.79 (.54–1.18)	.25	0.86[b] (.59–1.26)	.44	0.94[b] (.65–1.35)	.72
Length of ICU stay, HR[d]	1.84 (1.12–3.01)	.02	1.58 (.97–2.53)	.06	0.94 (.50–1.77)	.85
Length of hospital stay, HR[d]	1.08 (.90–1.29)	.39	0.98 (.82–1.17)	.83	1.03 (.87–1.23)	.72

Variables used for propensity score matching were sex, race, body mass index, medical condition (asthma, chronic lung disease, cardiovascular disease, chronic metabolic disease, neurologic disease, immunosuppression, hemoglobinopathy/blood disorders, renal disease, and liver disease), alcohol abuse status, and smoking status.

Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio.

[a] Admitted to the ICU or died.

[b] Adjusted for the Charlson comorbidity index.

[c] Among those who underwent chest radiography within 3 days of admission (n = 1460).

[d] HR represents ICU or hospital discharge.

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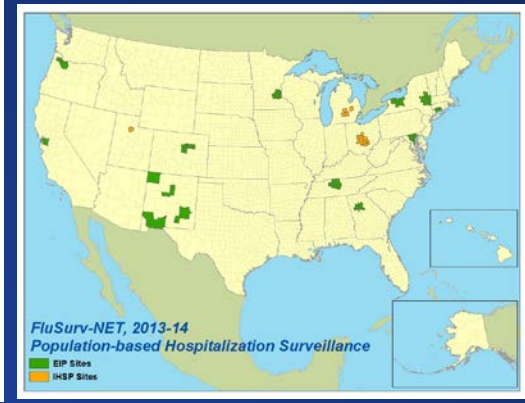
2009H1N1 predom.

Influenza Vaccination Modifies Disease Severity Among Community-dwelling Adults Hospitalized With Influenza

Carmen Arriola,[1] Shikha Garg,[1] Evan J Anderson,[2,3] Patrician A Ryan,[4] Andrea George,[5] Shelley M Zansky,[6] Nancy Bennett,[7] Arthur Reingold,[8] Marisa Bargsten,[9] Lisa Miller,[10] Kimberly Yousey-Hindes,[11] Lilith Tatham,[12] Susan R Bohm,[13] Ruth Lynfield,[14] Ann Thomas,[15] Mary Lou Lindegren,[16] William Schaffner,[16] Alicia M. Fry,[1] and Sandra S. Chaves[1]



Clin Infect Dis. 2017 Oct 15;65(8):1289-1297.

Table 2. Influenza Vaccination and Severity of Influenza Disease Analysis for the 2013–14 Season by Age Category, After Propensity Score Matching[a] and Adjusted for Timing of Antiviral Treatment and Time Seeking Hospital Care[b]

	Influenza Vaccine 2013–14 Season					
	18–49 years (n = 600)		50–64 years (n = 1186)		65+ years (n = 732) ×1000sim	
Clinical Outcomes	Point Estimate	(95% CI)	Point Estimate	(95% CI)	Point Estimate[c]	(95% CI)[c]
Admitted to ICU (OR)	0.63	(0.42; 0.93)	1.05	(0.80; 1.37)	0.63	(0.48; 0.81)
Deceased (OR)	0.21	(0.05; 0.97)	0.48	(0.24; 0.97)	0.39	(0.17; 0.66)
Pneumonia[d]	0.77	(0.52; 1.15)	1.10	(0.83, 1.46)	1.02	(0.81, 1.27)
Shorter ICU length of stay (RH)[e]	1.40	(0.97; 2.02)	1.36	(1.06; 1.74)	1.34	(1.06; 1.73)
Shorter hospital length of stay (RH)[e]	1.11	(0.95; 1.29)	1.13	(1.02; 1.26)	1.24	(1.13; 1.37)

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio; RH, relative hazard.

[a]Matched by age (subcategorized in age groups 18 to 29, 30 to 39 and 40 to 49, and 65 to 74 and 75+ for age categories 18–49 and 65+ years, respectively), sex, race, state, weight status based on Body Mass Index (BMI), chronic underlying conditions (asthma, chronic lung disease, cardiovascular disease, chronic metabolic disease, neurologic disease, immunosuppression, blood disorder, renal disease, liver disease, and having at least one of these conditions), and alcohol abuse and smoking.

[b]Timing for antiviral treatment was calculated from symptom onset and categorized as ≤2 days, 3–5 days, and >5 days or no treatment; time seeking hospital care (≤2 vs >2 days).

[c]Based on 1000 simulations; point estimate and lower and upper confidence interval represent 50th, 2.5th and 97.5th percentiles of point estimates (n = 1000), respectively.

[d]Pneumonia analysis was performed among those who had chest x-rays within 3 days of admission.

[e]RH represents ICU or hospital discharge accounting for death.

Do prior seasons of influenza vaccination impact the current season's vaccine effectiveness?

Influenza Vaccine Effectiveness in the 2011–2012 Season: Protection Against Each Circulating Virus and the Effect of Prior Vaccination on Estimates

Clinical Infectious Diseases 2014;58(3):319–27

Suzanne E. Ohmit,[1] Mark G. Thompson,[2] Joshua G. Petrie,[1] Swathi N. Thaker,[2] Michael L. Jackson,[3] Edward A. Belongia,[4] Richard K. Zimmerman,[5] Manjusha Gaglani,[7,8] Lois Lamerato,[9] Sarah M. Spencer,[2] Lisa Jackson,[3] Jennifer K. Meece,[4] Mary Patricia Nowalk,[5] Juhee Song,[7,8] Marcus Zervos,[9] Po-Yung Cheng,[2] Charles R. Rinaldo,[6] Lydia Clipper,[7] David K. Shay,[2] Pedro Piedra,[10] and Arnold S. Monto[1]

Table 5. Unadjusted and Adjusted Vaccine Effectiveness, Stratified by Combinations of Prior (2010–2011) and Current (2011–2012) Influenza Vaccination Status Among Patients Aged ≥9 Years

	Influenza-Positive Cases		Influenza-Negative Controls		Unadjusted		Adjusted[a]	
	No. Cases/ Row Total	Row %	No. Controls/ Row Total	Row %	VE %	(95% CI)	VE %	(95% CI)
Vaccinated current 2011–2012[b] only	42/512	8.2	470/512	91.8	61	(45 to 72)	56	(37 to 69)
Vaccinated current 2011–2012[b] and prior 2010–2011[c]	106/895	11.8	789/895	88.2	41	(26 to 54)	45	(27 to 58)
Vaccinated prior 2010–2011[c] only	45/277	16.3	232/277	83.8	15	(−19 to 40)	18	(−20 to 43)
Not vaccinated either 2010–2011 or 2011–2012	298/1597	18.7	1299/1597	81.3	Reference		Reference	

Vaccine effectiveness (100 × [1 − odds ratio]) was estimated by calculating the ratio of the odds of a specific vaccine exposure (current only, both current and prior, and prior only) among influenza positive cases to the odds of that vaccine exposure among influenza negative controls, relative to those unvaccinated in both years, in logistic regression models. The *P* value for the interaction of prior (2010–2011) and current (2011–2012) season vaccination status for patients aged ≥9 years was .03.

Abbreviations: CI, confidence interval; VE, vaccine effectiveness

[a] Models were adjusted for network center, subject age in months, sex, race/ethnicity categories, presence of high-risk health conditions, self-rated health status, time (days) between illness onset and specimen collection, and calendar time.

[b] Subjects were considered vaccinated in 2011–2012 if they had documented medical record or immunization registry evidence of receipt of at least 1 dose of influenza vaccine for the current (2011–2012) season ≥14 days before illness onset.

[c] Subjects were considered vaccinated in 2010–2011 if they had documented medical record or immunization registry evidence of receipt of at least 1 dose of influenza vaccine for the 2010–2011 season.

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

Clinical Infectious Diseases® 2016;63(8):1017–25

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

Table 4. Multiple Sensitivity Analyses of Influenza Vaccine Effectiveness (VE) in Preventing Influenza A (H3N2)–Related Hospitalization—Hospital VE: 2014–2015

Analysis Subset	Vaccinated Influenza Positive N/Total (%)	Unvaccinated Influenza Positive N/Total (%)	Unadjusted VE[a] % (95% CI)	Adjusted VE[a,b] % (95% CI)
Primary analysis[c]	57/421 (13.5)	41/203 (20.2)	38.2 (4.0, 60.3)	43.4 (4.9, 66.4)
Alternative definitions of vaccination status				
2-year vaccination history[d]	Vaccinated influenza positive N/Total (%)	Unvaccinated 2014–2015 and 2013–2014 Influenza positive N/Total (%)	Unadjusted VE[b] % (95% CI)	Adjusted VE[b,c] % (95% CI)
2014–2015 only	11/107 (10.3)	18/96 (18.8)	49.4 (−12.3, 77.2)	55.1 (−8.9, 81.5)
2014–2015 and 2013–2014	33/207 (15.9)	18/96 (18.8)	18.5 (−52.9, 56.6)	41.8 (−26.8, 73.3)
2013–2014 only	7/27 (25.9)	18/96 (18.8)	−55.2 (−318.8, 42.5)	−50.3 (−371.9, 52.2)

Abbreviation: CI, confidence interval; VE, vaccine effectiveness.

[a] Participants were considered vaccinated if documented or plausible self-reported influenza vaccine receipt was ≥14 days before illness onset; participants were considered unvaccinated if there was no evidence of documented vaccination and they self-reported no vaccination.

[b] VE% calculated as 100*(1 − odds ratio) in Firth penalized logistic regression models with profile likelihood CIs.

[c] Models were adjusted for hospital site (University of Michigan or Henry Ford), age in months, sex, frailty score, categorical Charlson comorbidity index, days between illness onset and specimen collection, and categorical biweekly calendar time of illness onset.

[d] Analyses of 2-year vaccination history were limited to those receiving regular care in the enrollment health system; prior season vaccine receipt was based on documented evidence only.

What about the new influenza vaccines (high dose and adjuvanted)?

Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults

Carlos A. DiazGranados, M.D., Andrew J. Dunning, Ph.D., Murray Kimmel, D.O., Daniel Kirby, B.Sc., John Treanor, M.D., Avi Collins, B.Sc.N., Richard Pollak, D.P.M., Janet Christoff, R.N., John Earl, M.D., Victoria Landolfi, M.Sc., M.B.A., Earl Martin, D.O., Sanjay Gurunathan, M.D., Richard Nathan, D.O., David P. Greenberg, M.D., Nadia G. Tornieporth, M.D., Michael D. Decker, M.D., M.P.H., and H. Keipp Talbot, M.D., M.P.H.

N Engl J Med 2014;371:635-45.

Table 1. Baseline Demographic and Clinical Characteristics of the High-Dose and Standard-Dose Vaccine Groups.*

Characteristic	IIV3-HD (N=15,990)	IIV3-SD (N=15,993)
Female sex — no. (%)	9,131 (57.1)	8,963 (56.0)
Mean age — yr	73.3±5.8	73.3±5.8
Racial background — no. (%)†		
White	15,103 (94.4)	15,167 (94.8)
Asian	118 (0.7)	105 (0.7)
Black	670 (4.2)	612 (3.8)
Other	97 (0.6)	106 (0.7)
Hispanic ethnic group — no. (%)†	958 (6.0)	982 (6.1)
At least one prespecified chronic coexisting condition — no. (%)‡	10,750 (67.2)	10,752 (67.2)
At least two prespecified chronic coexisting conditions — no. (%)	5,385 (33.7)	5,403 (33.8)
Cardiac and respiratory disorders — no. (%)		
Coronary artery disease	2,735 (17.1)	2,732 (17.1)
Atrial fibrillation	1,103 (6.9)	1,112 (7.0)
Valvular heart disease	744 (4.6)	741 (4.6)
Congestive heart failure	451 (2.8)	446 (2.8)
Chronic obstructive lung disease	1,500 (9.4)	1,495 (9.4)
Asthma	1,415 (8.8)	1,408 (8.8)
Received influenza vaccine the previous season — no. (%)	11,758 (73.5)	11,773 (73.6)

Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults

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N Engl J Med 2014;371:635-45.

Table 4. Hemag Types and Subtypes Contained in the Vaccine.*

Viral Type/ Subtype	Combined†		
	IIV3-HD (N=5254)	IIV3-SD (N=5254)	IIV3-HD vs. IIV3-SD
	geometric mean titer (95% CI‡)		*ratio of geometric mean titers (95% CI‡)*
A/H1N1	439.2 (425.1–453.8)	246.6 (237.9–255.6)	1.8 (1.7–1.9)
A/H3N2			
B			
	% with seroprotection (95% CI§)		*percentage-point difference (95% CI¶)*
A/H1N1	98.5 (98.1–98.8)	93.7 (93.0–94.3)	4.8 (4.1–5.5)
A/H3N2			
B			

*The number of p immunogenicity subset who had at least one hemagglutination inhibiti

†The type A (H1 ne, but the type A (H3N2) and type B viruses used to make the 2012– he type A (H1N1) strain can be combined.

‡The geometric m titer) follows a normal distribution.

§The confidence

¶The confidence

Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults

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N Engl J Med 2014;371:635-45.

Table 2. Efficacy of High-Dose Vaccine Relative to Standard-Dose Vaccine against Confirmed Influenza Caused b

Variable	Laboratory-Confirmed Influenza†		
	IIV3-HD (N=15,990)	IIV3-SD (N=15,993)	Relative Efficacy (95% CI)
	no. (%)		%
Protocol-defined influenza-like illness	228 (1.4)	301 (1.9)	24.2 (9.7 to 36.5)‡
Influenza A	190 (1.2)	250 (1.6)	24.0 (7.8 to 37.4)
A/H1N1	8 (<0.1)	9 (0.1)	11.1 (–159.6 to 70.2)
A/H3N2	171 (1.1)	223 (1.4)	23.3 (6.0 to 37.5)
Influenza B	38 (0.2)	51 (0.3)	25.5 (–15.7 to 52.4)

NNT 220

Efficacy, immunogenicity, and safety evaluation of an MF59-adjuvanted quadrivalent influenza virus vaccine compared with non-adjuvanted influenza vaccine in children: a multicentre, randomised controlled, observer-blinded, phase 3 trial

Timo Vesikari, Judith Kirstein, Grace Devota Go, Brett Leav, Mary Ellen Ruzycky, Leah Isakov, Marianne de Bruijn, Janine Oberye, Esther Heijnen

Lancet Respir Med 2018; 6: 345–56

Summary

Background Young children have immature immune systems and respond poorly to standard influenza vaccines. The oil-in-water emulsion adjuvant MF59 can increase antigen uptake, macrophage recruitment, lymph node

	N		GMT		GMT ratio (95% CI)
	aIIV4	Comparator	aIIV4	Comparator	
Participants aged 6 months through 5 years					
A/H1N1	1362	1307	996·40	522·50	1·91 (1·8–2·0)
A/H3N2	1362	1307	1153·4	674·01	1·71 (1·6–1·8)
B/Yamagata	1362	1307	198·89	90·68	2·19 (2·0–2·4)
B/Victoria*	745	738	315·52	138·82	2·27 (2·0–2·6)
Participants aged 6 through 23 months and 2 through 5 years					
A/H1N1					
6 through 23 months	378	384	654·99	223·88	2·93 (2·5–3·5)
2 through 5 years	984	923	1110·84	692·98	1·60 (1·5–1·8)
A/H3N2					
6 through 23 months	378	384	982·98	380·79	2·58 (2·2–3·0)
2 through 5 years	984	923	1261·91	862·17	1·46 (1·3–1·6)
B/Yamagata					
6 through 23 months	378	384	130·25	35·89	3·63 (3·1–4·3)
2 through 5 years	984	923	200·09	111·83	1·79 (1·6–2·0)
B/Victoria*					
6 through 23 months	167	179	292·45	76·07	3·84 (2·9–5·0)
2 through 5 years	578	559	322·52	168·31	1·92 (1·6–2·2)

Figure 2: GMTs and vaccine group ratios against homologous vaccine strains 21 days after last vaccination for the immunogenicity full analysis set

Efficacy, immunogenicity, and safety evaluation of an MF59-adjuvanted quadrivalent influenza virus vaccine compared with non-adjuvanted influenza vaccine in children: a multicentre, randomised controlled, observer-blinded, phase 3 trial

	Age 6 through 23 months			Age 2 through 5 years		
	aIIV4 (n=1299)	Comparator† (n=1339)	Relative vaccine efficacy‡ (95% CI)	aIIV4 (n=3979)	Comparator† (n=3854)	Relative vaccine efficacy‡ (95% CI)
RT-PCR-confirmed influenza						
Any strain§	55 (4%)	79 (6%)	31·37 (3·14 to 51·38)	201 (5%)	173 (4%)	−14·99 (−40·93 to 6·18)
A/H1N1	2 (<1%)	5 (<1%)	NA¶	5 (<1%)	12 (<1%)	NA¶
A/H3N2	44 (3%)	66 (5%)	34·50 (4·05 to 55·28)	156 (4%)	130 (3%)	−19·28 (−50·57 to 5·51)
B/Yamagata	5 (<1%)	9 (1%)	NA¶	31 (1%)	27 (1%)	−11·25 (−86·42 to 33·61)
B/Victoria‖	4 (<1%)	0	NA¶	10 (<1%)	9 (<1%)	NA¶
Culture-confirmed influenza						
Any strain§	31 (2%)	48 (4%)	35·96 (−0·63 to 59·25)	109 (3%)	98 (3%)	−9·18 (−43·44 to 16·90)
A/H1N1	1 (<1%)	4 (<1%)	NA¶	4 (<1%)	5 (<1%)	NA¶
A/H3N2	23 (2%)	38 (3%)	40·23 (−0·35 to 64·40)	73 (2%)	66 (2%)	−8·95 (−52·02 to 21·91)
B/Yamagata	5 (<1%)	7 (1%)	NA¶	24 (1%)	20 (1%)	−16·84 (−111·54 to 35·47)
B/Victoria‖	2 (<1%)	0	NA¶	8 (<1%)	8 (<1%)	NA¶
Matched**	19 (1%)	32 (2%)	40·92 (−4·27 to 66·52)	55 (1%)	48 (1%)	−12·16 (−65·19 to 23·85)
Unmatched**	12 (1%)	14 (1%)	13·51 (−87·08 to 60·01)	53 (1%)	48 (1%)	−8·26 (−60·01 to 26·75)

Data are n (%), unless otherwise stated. aIIV4=MF59-adjuvanted, quadrivalent, subunit inactivated influenza vaccine. NA=not applicable. IIV3=trivalent inactivated influenza vaccine. IIV4=quadrivalent inactivated influenza vaccine. *Includes participants from seasons one and two who received at least one dose of study vaccination and provided efficacy endpoint data. †The comparator was non-adjuvanted IIV3 in season one and non-adjuvanted IIV4 in season two. ‡Result is based on the Cox proportional hazards model for time until onset of the first confirmed influenza, adjusting for vaccine naivety, risk factor, season, dose group, and country as random effect. §Any strain regardless of antigenic match. For any participant who had multiple confirmed influenza infections, only the first-occurrence confirmation was included under any strain. However, for all confirmed influenza infections, the first occurrence for each strain was counted separately under each respective individual confirmed strain. Therefore, the sum of cases under each strain can be higher compared with the total number of cases reported under any strain. ¶Per the statistical analysis plan, relative vaccine efficacy was not calculated if number of cases was less than 20. ‖B/Victoria cases from season one have not been included in the analysis. **Matched strains are those with a less than eight-fold difference in titre and unmatched strains are those with eight-fold difference or more in titre compared with the vaccine strain.

Table 3: First-occurrence RT-PCR-confirmed and culture-confirmed influenza and relative vaccine efficacy in participants aged 6 through 23 months and 2 through 5 years*

FluAd PI

https://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM474387.pdf

Table 1: Percentages of Subjects ≥ 65 Years of Age With Solicited Local and Systemic Adverse Reactions in Days 1-7 After Administration of FLUAD or AGRIFLU (a U.S. Licensed Comparator) NCT01162122

Study 1			
		FLUAD (N[a]=3418-3496) Percentage	AGRIFLU (N[a]=3420-3488) Percentage
Local			
Injection site Pain	Any	25.0	12.2
	Moderate[b]	3.9	1.9
	Severe[c]	0.3	0.2
Tenderness	Any	21.1	11.2
	Moderate	3.0	1.0
	Severe	0.1	0.2
Erythema	Any	1.2	0.5
	25 to ≤ 50 mm	1.1	0.5
	51 to ≤ 100 mm	0.2	<0.1
	> 100 mm	0.0	0.0
Induration	Any	1.3	0.5
	25 to ≤ 50 mm	1.0	0.5
	51 to ≤ 100 mm	0.3	0.0
	> 100 mm	0.0	0.0
Swelling	Any	1.2	0.4
	25 to ≤ 50 mm	1.0	0.4
	51 to ≤ 100 mm	0.2	<0.1
	> 100 mm	0.0	0.0

Table 2: Immune Responses to Each Antigen 22 Days after Vaccination with FLUAD or AGRIFLU in Adults 65 Years and Older[a]

	FLUAD	AGRIFLU	
GMTs Against	**GMT N[b]= 3225-3227 (95% CI)**	**GMT N[b] =3256-3259 (95% CI)**	**GMT Ratio[c] (95% CI)**
A/California/7/2009-like (H1N1)	99 (93-106)	70 (66-75)	1.4 (1.32-1.49)
A/Perth/16/2009-like (H3N2)	272 (257-288)	169 (159-179)	1.61 (1.52-1.7)
B/Brisbane/60/2008-like	28 (26-29)	24 (23-26)	1.15 (1.08-1.21)

What are the net benefits of influenza vaccination?

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

Influenza Disease and Vaccination

- 3 – 57,000 deaths/year
  - Median ~22,000 deaths/year
- Flu vaccine ~50% effective in prevention
- What other public health intervention has similar effectiveness and burden?

Motor Vehicle Safety
State Data and Information +
Cost Data and Prevention Policies +
Child Passenger Safety +
Seat Belts −
Get the Facts
State Fact Sheets
What Works: Strategies to Increase Restraint Use
State Data
Seat Belt Use US Map
Publications

CDC > Motor Vehicle Safety > Seat Belts

Seat Belts: Get the Facts

Language: English (US)

The Problem | Risk Factors | Effectiveness | Prevention | Additional Resources

How big is the problem of crash-related injuries and deaths to drivers and passengers?

Motor vehicle crashes are a leading cause of death among those aged 1-54 in the U.S.[1] Most crash-related deaths in the United States occur to passenger vehicle occupants (drivers and passengers).[2]

For adults and older children (who are big enough for seat belts to fit properly), seat belt use is one of the most effective ways to save lives and reduce injuries in crashes.[3] Yet millions do not buckle up on every trip.[4]

Deaths

- A total of 22,441 passenger vehicle occupants died in motor vehicle traffic crashes in 2015.[2]

Motor Vehicle Safety

Motor Vehicle Safety
State Data and Information +
Cost Data and Prevention Policies +
Child Passenger Safety +
Seat Belts −
Get the Facts
State Fact Sheets
What Works: Strategies to Increase Restraint Use

CDC > Motor Vehicle Safety > Seat Belts

Seat Belts: Get the Facts

Language: English (US)

The Problem | Risk Factors | **Effectiveness** | Prevention | Additional Resources

What is the impact of seat belt use?

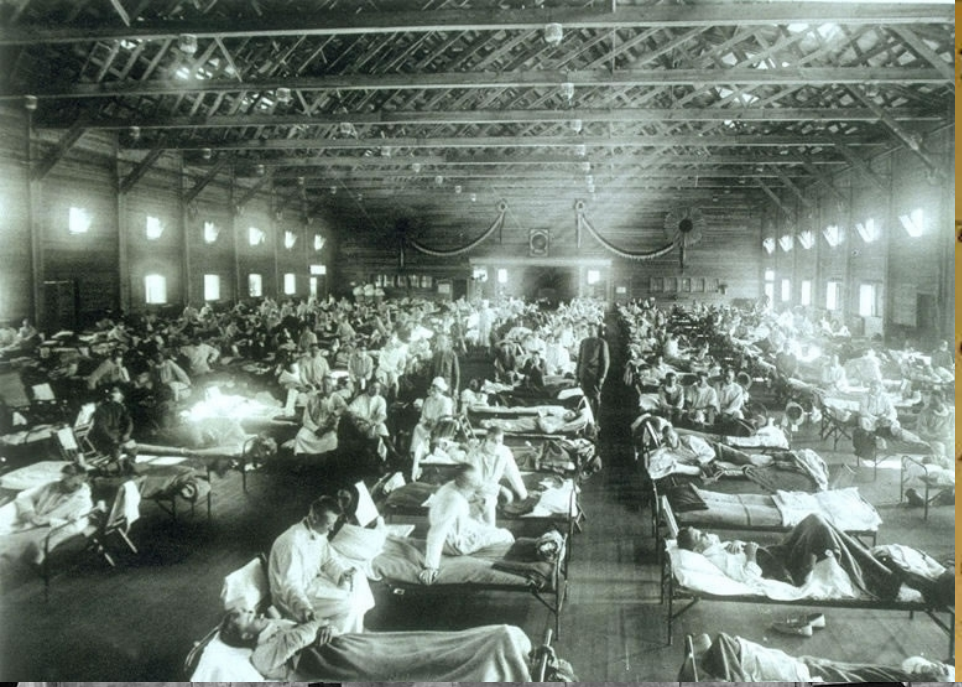
- Seat belts reduce serious crash-related injuries and deaths by about half.[12]
- Seat belts saved almost 14,000 lives in 2015.[3]
- Air bags provide added protection but are not a substitute for seat belts. Air bags plus seat belts provide the greatest protection for adults.[13]

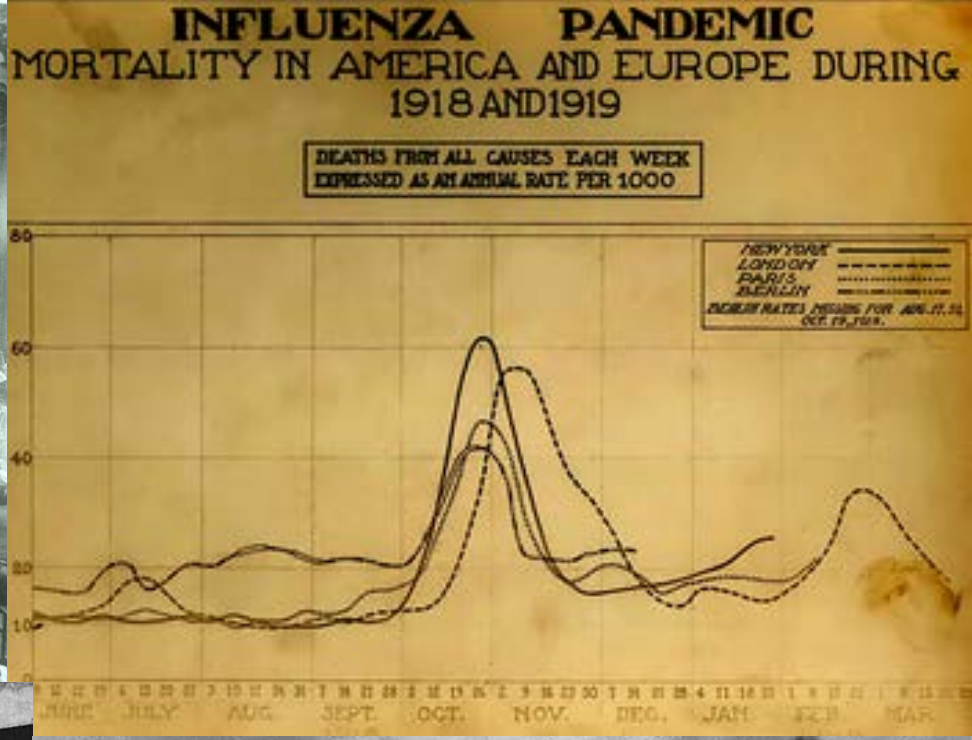
Pandemic Preparedness

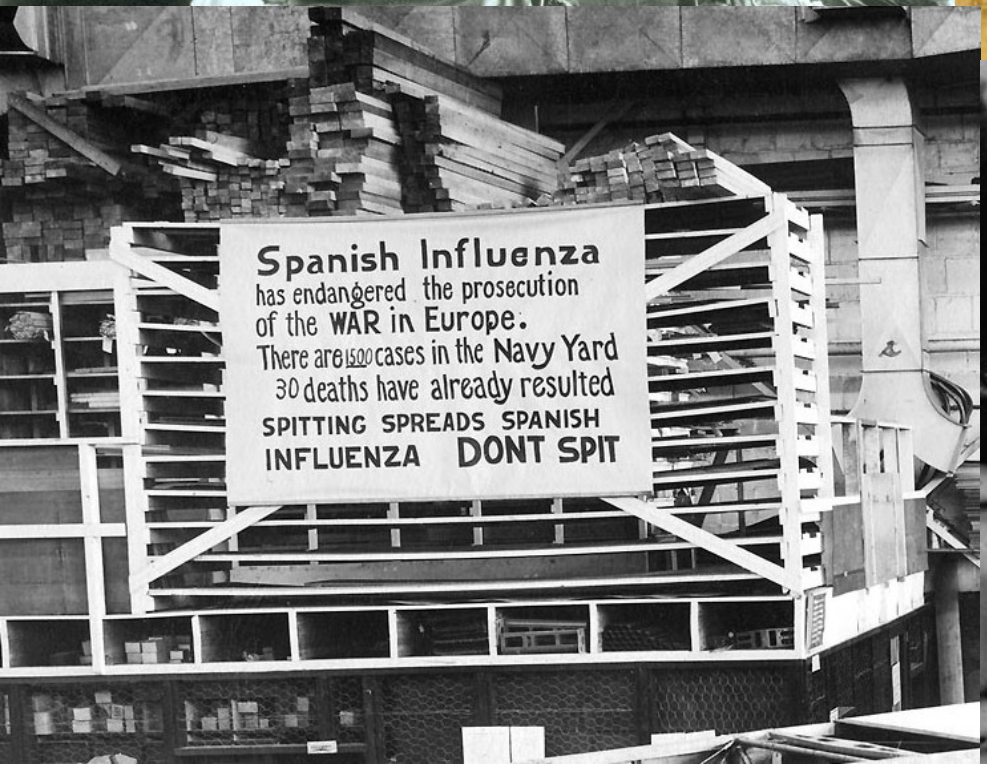
1918
FLU
PANDEMIC
100 YEARS

WE REMEMBER. WE PREPARE.

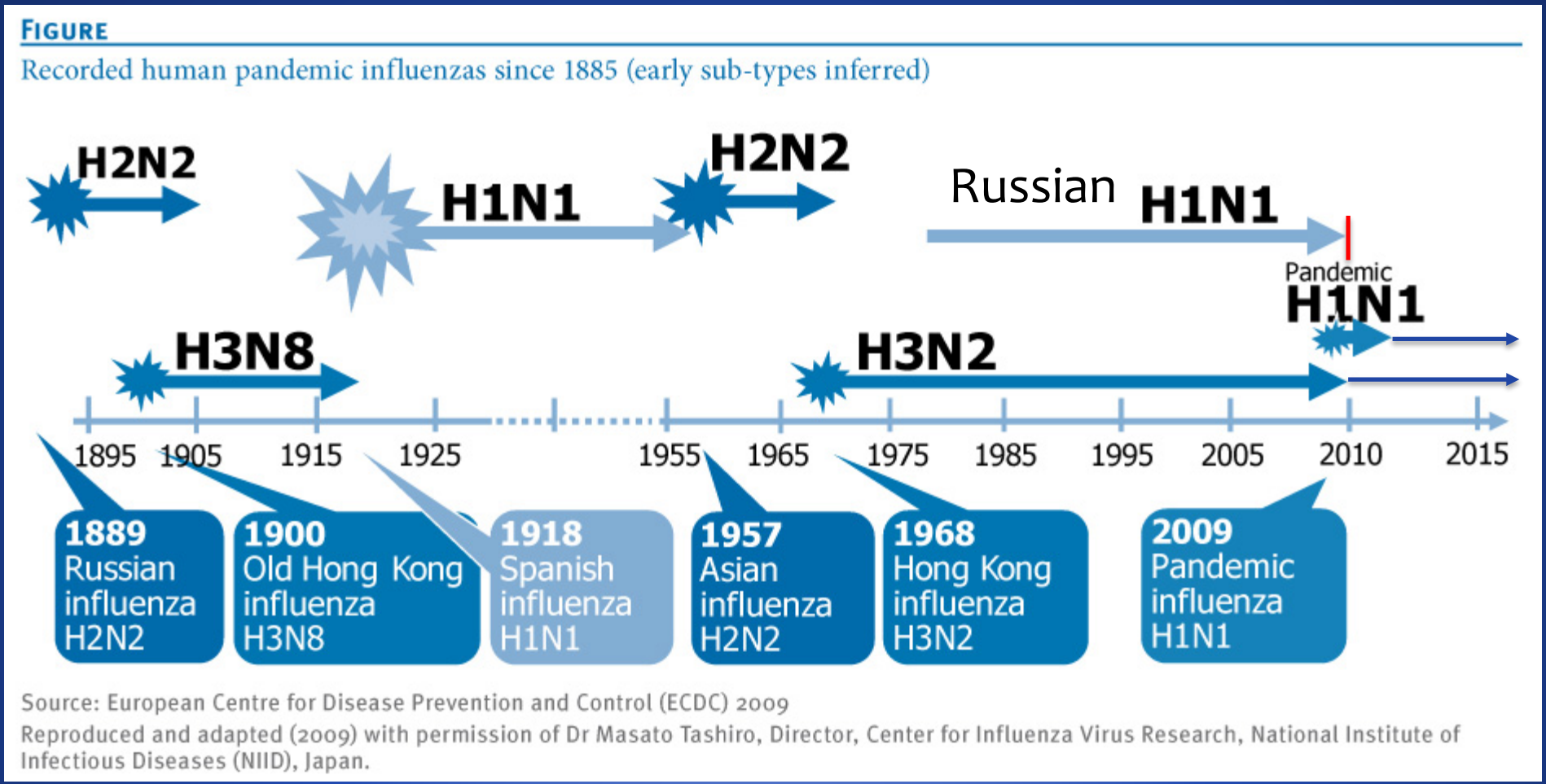
https://www.cdc.gov/flu/pandemic-resources/1918-commemoration/historical-images.htm



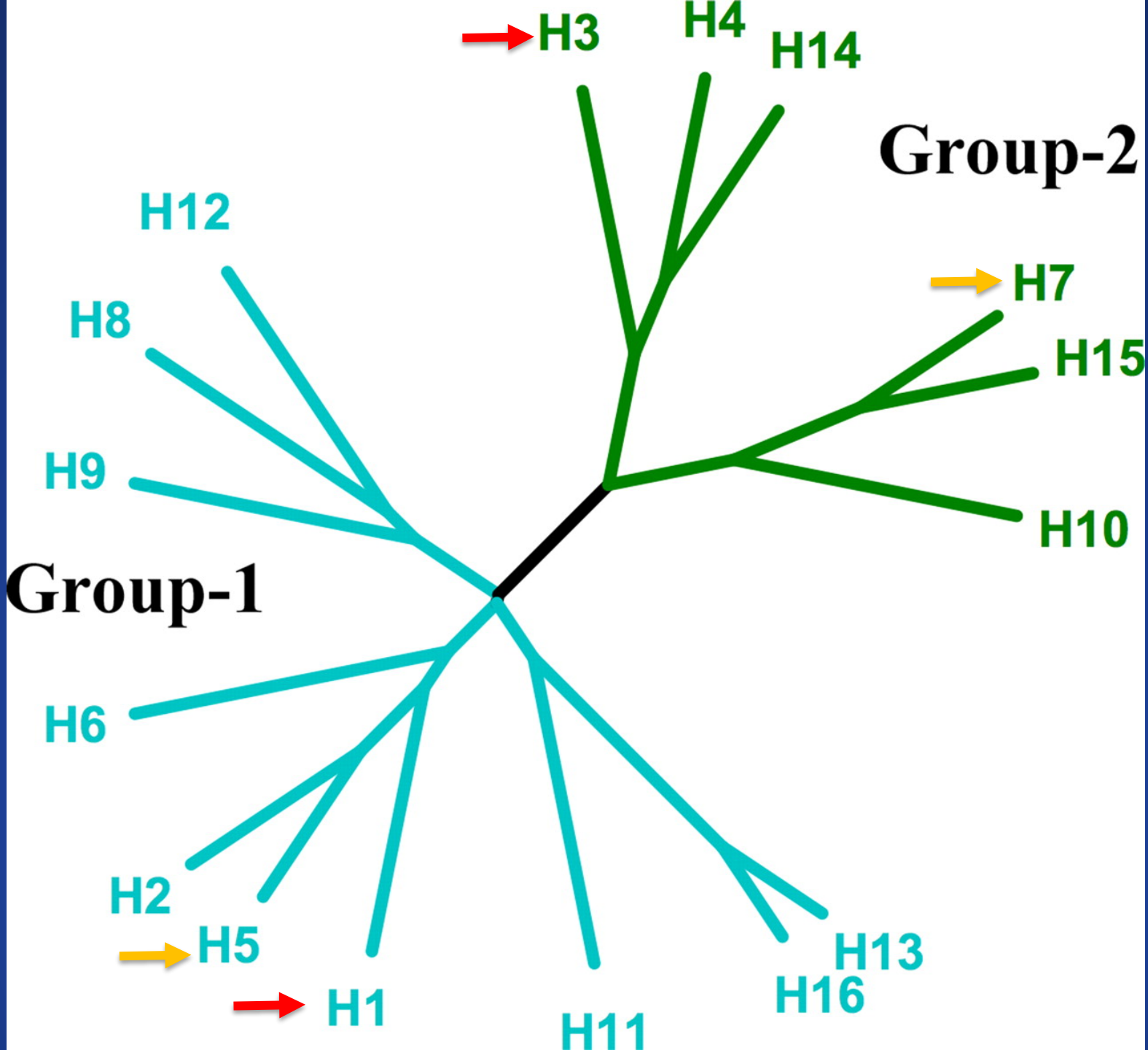

INFLUENZA PANDEMIC
MORTALITY IN AMERICA AND EUROPE DURING 1918 AND 1919
DEATHS FROM ALL CAUSES EACH WEEK EXPRESSED AS AN ANNUAL RATE PER 1000
NEW YORK
LONDON
PARIS
BERLIN
80
60
40
20
1.0
JULY
AUG.
SEPT.
OCT.
NOV.
DEC.
JAN.
FEB.
MAR.


Spanish Influenza
has endangered the prosecution
of the WAR in Europe.
There are 1500 cases in the Navy Yard
30 deaths have already resulted
SPITTING SPREADS SPANISH
INFLUENZA DONT SPIT

Antigenic Shift



https://www.csems.org/wp-content/uploads/2017/02/pan_flu_graphic.jpg


H3
H4
H14
Group-2
H12
H7
H8
H15
H9
H10
Group-1
H6
H2
H5
H13
H1
H16
H11

Antigenic Shift

TIMELINE OF EVENTS IN THE U.S.

Washington 1/3
California 1/23
Oregon 12/19/14
Idaho 1/16
Arkansas 3/11
South Dakota 4/1
Wisconsin 4/11
Minnesota 3/5
Missouri 3/27
Iowa 4/14
Indiana 5/10
Michigan 6/6
New Mexico 3/24
Kentucky 4/28

DEC 2014 | JAN 2015 | FEB 2015 | MAR 2015 | APR 2015 | MAY 2015 | JUN 2015

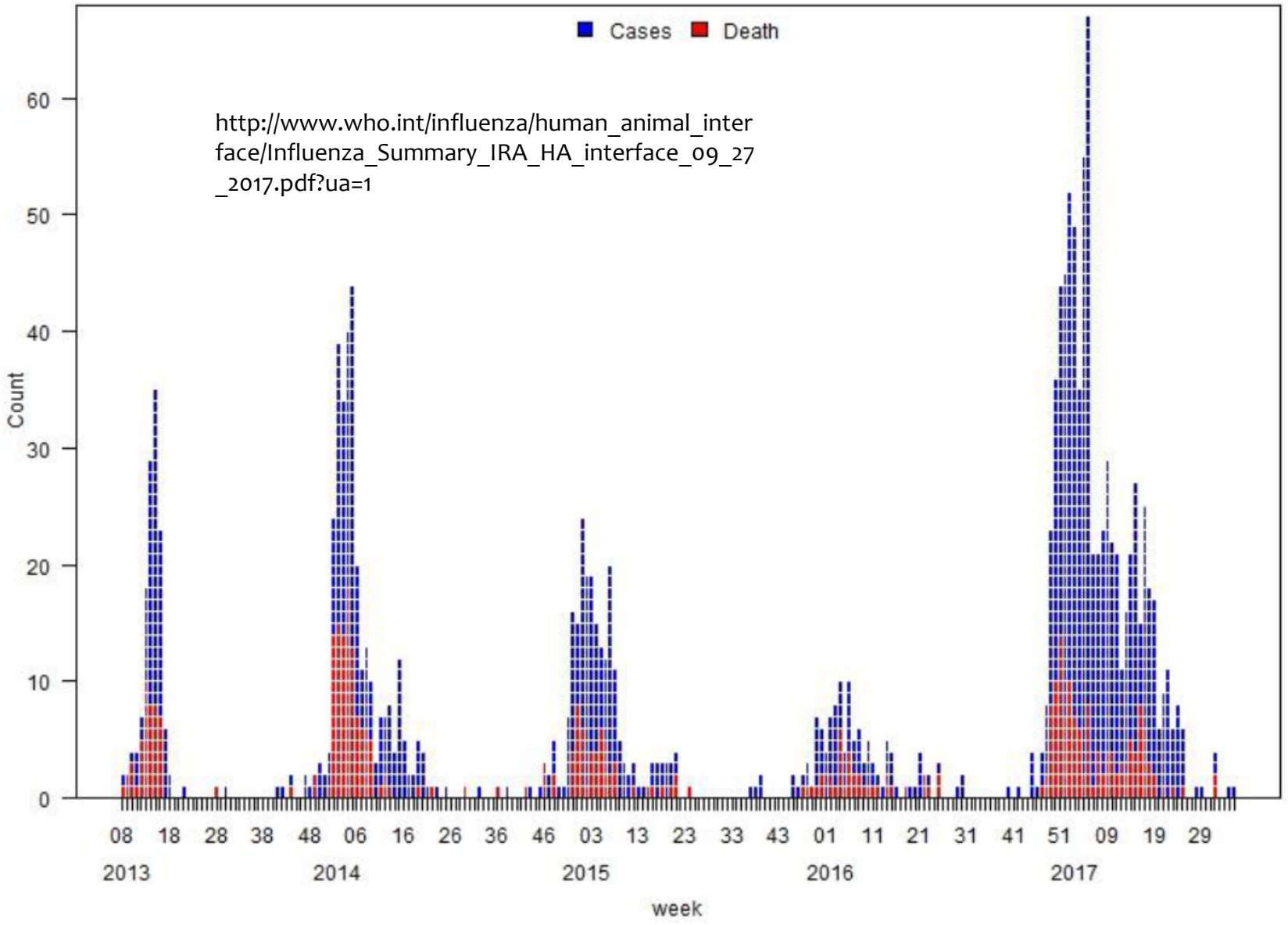
North Dakota 4/10
Wyoming 3/25
Nebraska 5/12
Utah 1/9
Nevada 1/30
Kansas 3/13
23 APR 2015
Minnesota declared a state of emergency.
Montana 3/27
JAN 2015
An HPAI H5N1 virus was first detected in a wild duck in the United States.
14 MAY 2015
Nebraska declared a state of emergency.
20 APR 2015
Wisconsin declared a state of emergency.
01 MAY 2015
Iowa declared a state of emergency.
16 DEC 2014
USDA/APHIS first reported the presence of highly pathogenic avian influenza (HPAI) H5N2 and HPAI H5N8 in wild birds in a few states.

Source: The United States Department of Agriculture/Animal and Plant Health Inspection Service (USDA/APHIS)

= First detection of avian flu.

H5 Influenza in bird population

Figure 1: Epidemiological curve of avian influenza A(H7N9) cases in humans by week of onset, 2013-2017.



Areas of Uncertainty in Influenza Vax

- Development of initial influenza response (to infection or vaccine) may result in some degree of imprinting. This imprinting may continue to impact responses for remainder of life (Original Antigenic Sin or OAS)

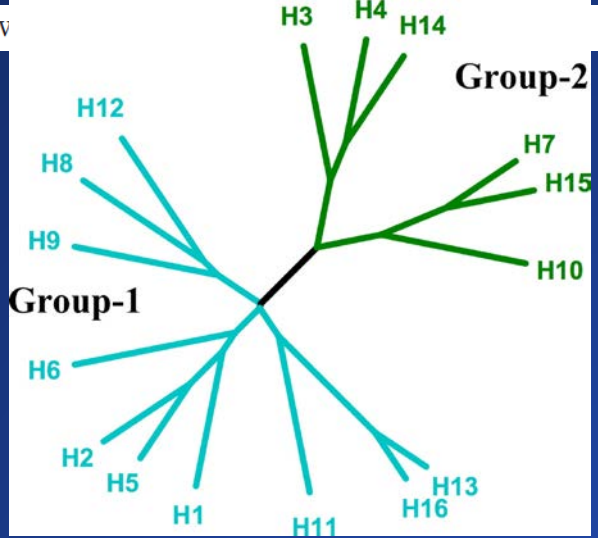
RESEARCH ARTICLE

INFLUENZA EPIDEMIOLOGY

Potent protection against H5N1 and H7N9 influenza via childhood hemagglutinin imprinting

Katelyn M. Gostic,[1] Monique Ambrose,[1] Michael Worobey,[2]* James O. Lloyd-Smith[1,3]*

Two zoonotic influenza A viruses (IAV) of global concern, H5N1 and H7N9, exhibit unexplained differences in age distribution of human cases. Using data from all known human cases of these viruses, we show that an individual's first IAV infection confers lifelong protection against severe disease from novel hemagglutinin (HA) subtypes in the same phylogenetic group. Statistical modeling shows that protective HA imprinting is the crucial explanatory factor, and it provides 75% protection against severe infection and 80% protection against death for both H5N1 and H7N9. Our results enable us to predict age distributions of severe disease for future pandemics and demonstrate that a novel strain's pandemic potential increases yearly when a group-mismatched HA subtype dominates seasonal influenza circulation. These findings open new frontiers for rational pandemic risk assessment.



RESEARCH ARTICLE

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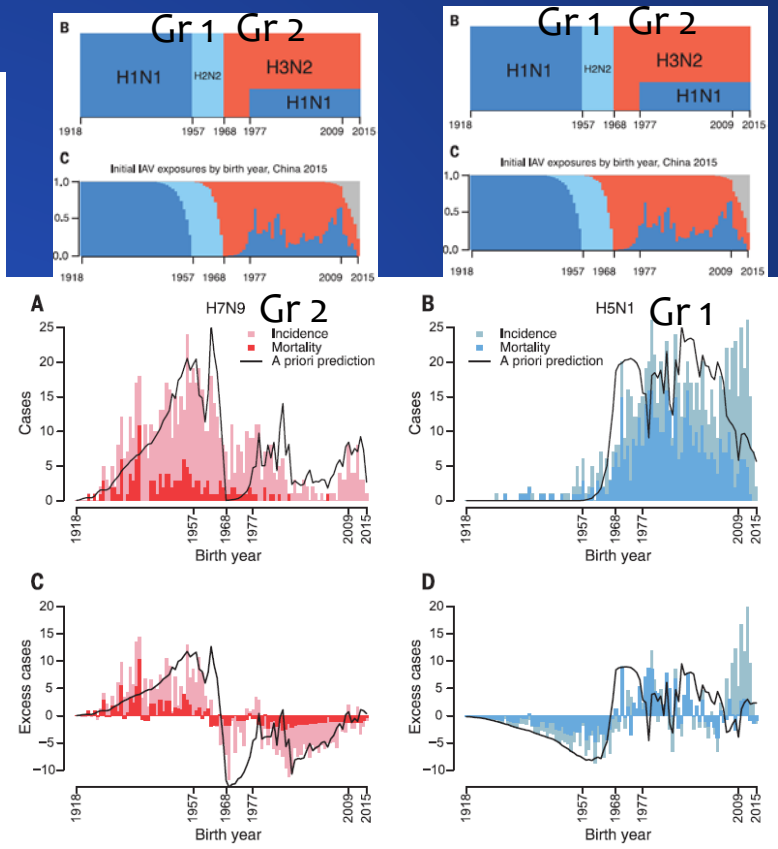

Fig. 2. H7N9 and H5N1 observed cases and deaths by birth year. Black lines show a priori predictions based on demographic age distribution and reconstructed patterns of HA imprinting. (**A**) 680 H7N9 cases from China, 2013–2015, and (**B**) 835 H5N1 cases from Cambodia, China, Egypt, Indonesia, Thailand, and Vietnam, 1997–2015. (**C** and **D**) Case data normalized to demographic age distribution from appropriate countries and case observation years.

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GEORGIA EIP emerging infections program

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GEORGIA EIP emerging infections program

Thanks for all you do…

- Efforts to improve influenza testing
- Timely reporting of hospitalized cases
- Submission of influenza isolates – maybe influenza vaccine virus next year will be…

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  A/Georgia/39/2019 (H3N2)