

INFLUENZA EPIDEMIOLOGY AND INFLUENZA VACCINES

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CONFLICTS OF INTEREST

- Dr. Zimmerman: None active. Within one year, research grants from Merck (adolescent vaccine) and Sanofi Pasteur
- Primarily federally funded





1918 INFLUENZA PANDEMIC

- Dr. Victor Vaughn, acting surgeon general of the army, receives urgent orders to proceed to Camp Devens. Once there, what Vaughn sees changes his life forever:
 - "I saw hundreds of young stalwart men in uniform coming into the wards of the hospital. Every bed was full, yet others crowded in. The faces wore a bluish cast; a cough brought up the blood-stained sputum. In the morning, the dead bodies are stacked about the morgue like cordwood."
- On that day at Camp Devens, 63 men died from influenza.



1918 PANDEMIC

- 25% attack rate in US
- Lowered US life expectancy by 12 years
- 10%-20% fatality rate among infected
- Killed 50 million worldwide
 - More than any other pandemic in known history



GLOBAL INFLUENZA PANDEMIC: ESTIMATED IMPACT IN UNITED STATES

- In the absence of any control measures (vaccination or drugs), expert estimates of a “medium–level” pandemic:
 - 15% and 35% of the U.S. population could be affected
 - 18 million to 42 million require outpatient visits, with another 20 million to 47 million sick people
 - 314,000 to 734,000 hospitalized
 - 89,000-207,000 deaths
 - Overall economic impact: \$71.3 billion to \$166.5 billion

- Due to antigenic shift

Source: <http://www.cdc.gov/flu/avian/gen-info/pandemics.htm>

WHEN WILL THE NEXT PANDEMIC OCCUR?

- New strain with little experience or resistance among humans
- Highly communicable
- Reassortment between animals and humans
 - Communicability from human strain; high pathogenicity from animal strain
- Reassortment could occur in a human infected with a human and an animal strain
 - Or, in an animal infected with both human and animal strains
 - Or, as a mutation in an animal strain that allows transmission among humans

AVIAN FLU

- H7N9 infections in people and poultry in China
- Sporadic infections in people; most with poultry exposure
- Rare limited person-to-person spread
- No sustained or community transmission
- High mortality: 359 of 918 known infections



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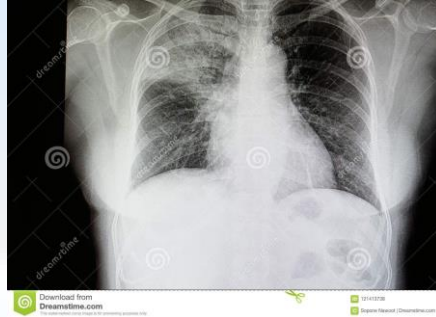
<http://en.chinabroadcast.cn/2239/2005-1-28/88@201395.htm>

3 TRANSMISSION MODES: LARGE DROPLET, SMALL DROPLET, HAND/FOMITE

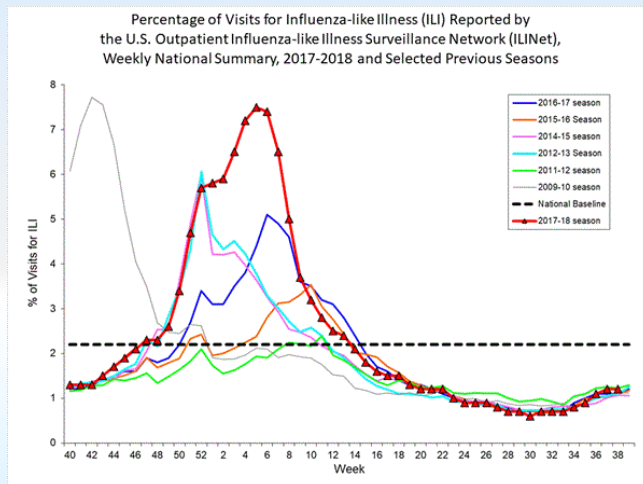


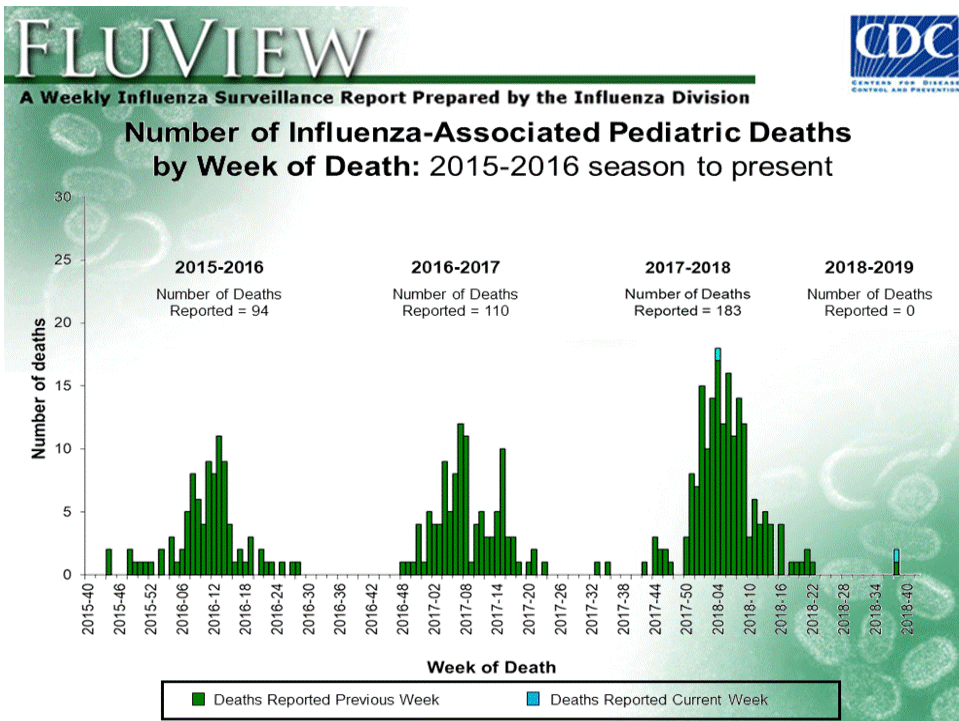
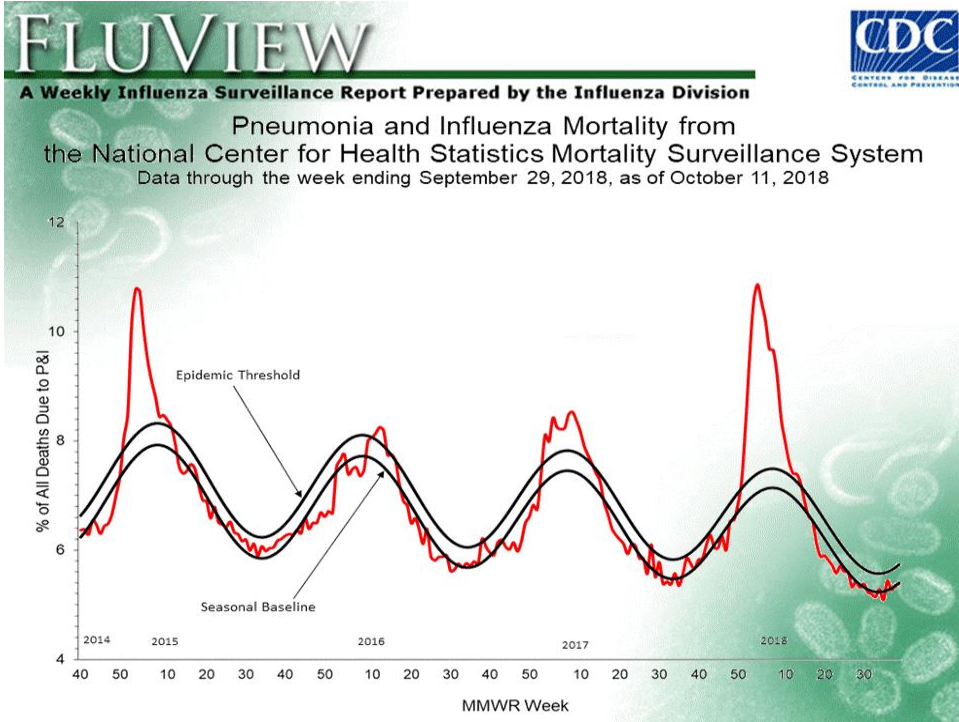
INFLUENZA COMPLICATIONS

- Pneumonia
 - primary influenza
 - secondary bacterial
- Reye syndrome
- Myocarditis, MI
- Worsening of chronic respiratory and cardiac diseases
- Death 0.5-1 per 1000 cases



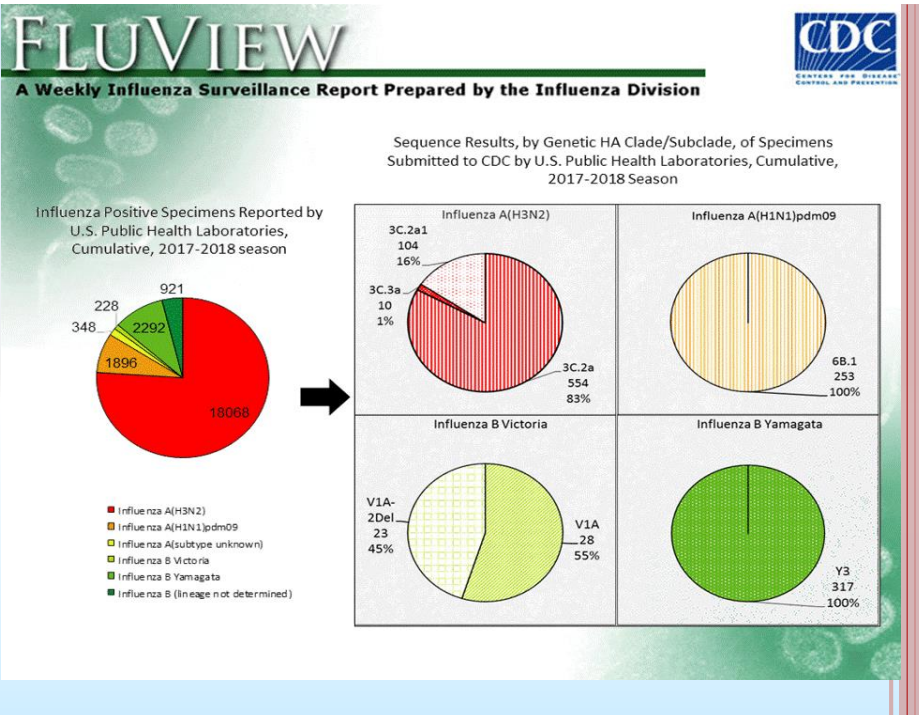
SURVEILLANCE ACTIVITY

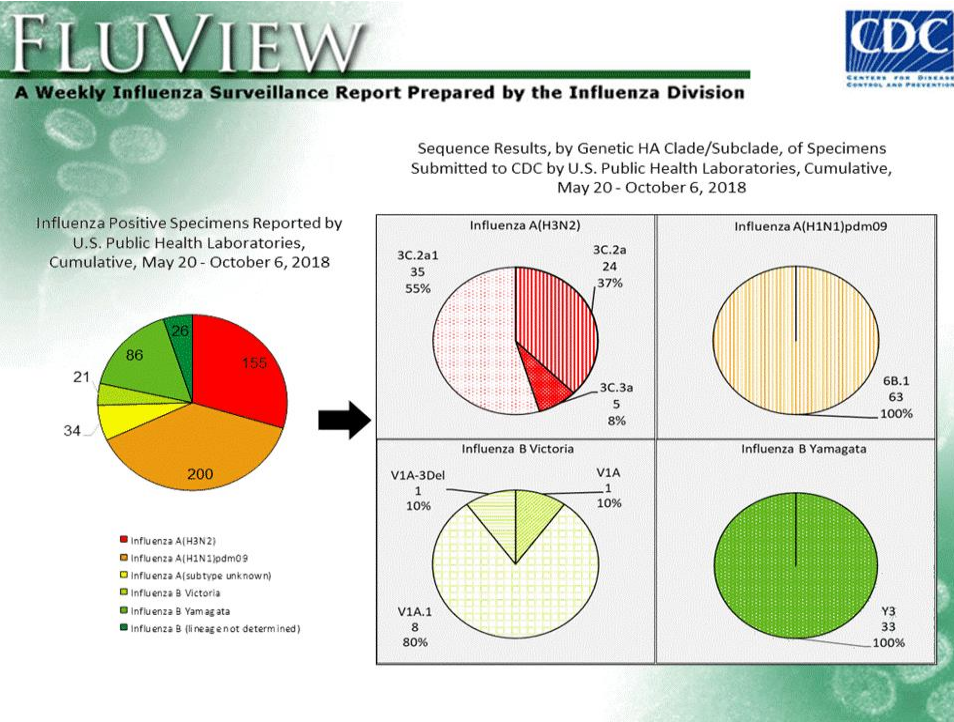




2017-2018 FLU DEATHS - CDC

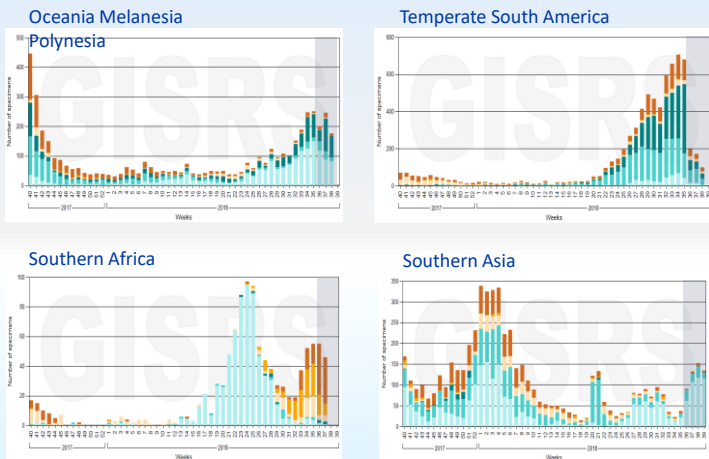
- **CDC Estimates of Hospitalizations and Deaths during 2017-2018**
 - More than 900,000 hospitalizations and more than 80,000 flu deaths
 - Previous highest numbers were 710,000 hospitalizations and 56,000 deaths in 2010





INFLUENZA TRANSMISSION ZONES

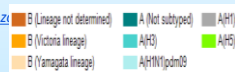
2017-2018: NUMBER OF INFLUENZA-POSITIVE CASES BY EPIDEMIOLOGIC WEEK AND SUBTYPE



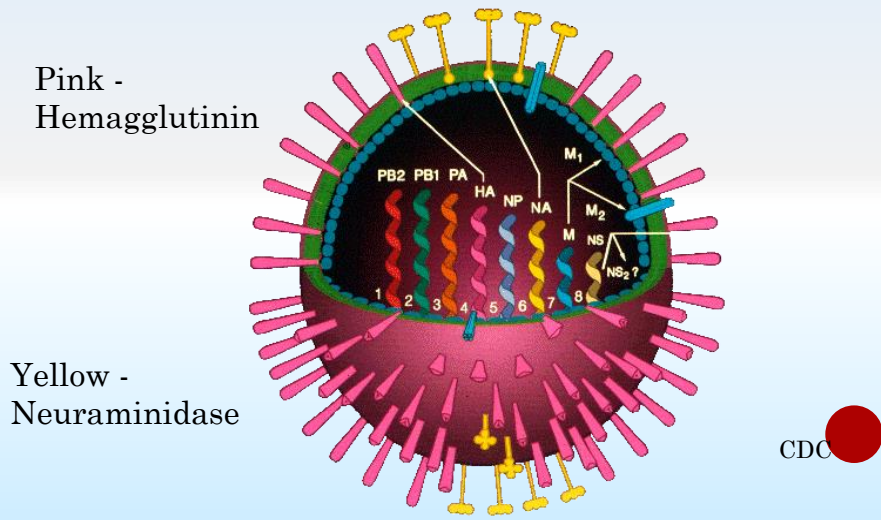
Source: WHO FluNet. For more information about influenza transmission zones:

http://www.who.int/csr/disease/swineflu/influenza_transmission_zones.pdf

• Data are through October 6, 2018



Influenza Virus



INFLUENZA ANTIGENIC CHANGES

- Hemagglutinin and neuraminidase antigens change with time
- Changes occur as a result of point mutations in the virus gene, or due to exchange of a gene segment with another subtype of influenza virus
- Impact of antigenic changes depend on extent of change (more change usually means larger impact)

INFLUENZA ANTIGENIC CHANGES

- Antigenic Shift
 - Major change, new subtype
 - Caused by exchange of gene segments
 - May result in pandemic

- Example of antigenic shift
 - H2N2 virus circulated in 1957-1967
 - H3N2 virus appeared in 1968 and completely replaced H2N2 virus



INFLUENZA VACCINE OPTIONS BY AGE - CHILDREN

Age group years	IIV: Fluzone* FluLaval * Fluarix	IIV: Afluria Quad*	Cell- culture Flucelvax *	LAIV	IIV: Afluria
6mo-2 years	X	X			
2-3 yrs	X	X		X	
4 years	X	X	X	X	X
5-18 yrs	X	X	X	X	X
Egg-free			X		
Valency	4	4	4	4	3

*Multidose vials of these products contain thimerosal (mercury derivative) as preservative. Single dose vials or syringes do not contain thimerosal.



INFLUENZA VACCINE OPTIONS BY AGE

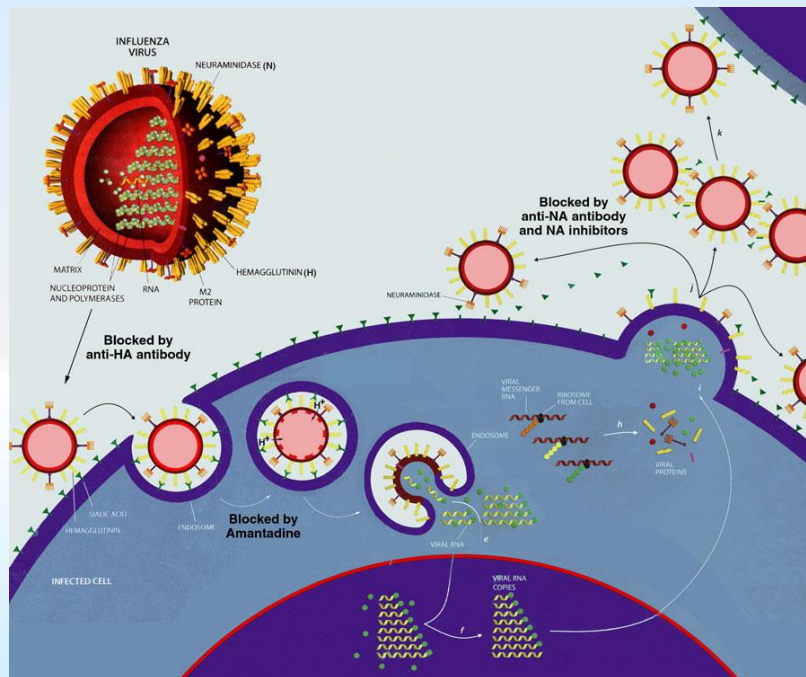
Age group years	IIV	Recombinant (RIV)	Cell-culture IIV	LAIV	IIV High Dose	IIV adjuvanted
18-49	X	X	X	X		
50-64	X	X	X			
≥65	X	X	X		X	X
Egg-free		X	X			
Valency	3-4	4	4	4	3	3

RIV = FluBlok

Cell-culture = Flucelvax

IIV adjuvanted = Flud

IIV High Dose = Fluzone HD



WHY QUADRIVALENT?

- Two type B lineages: Victoria and Yamagata

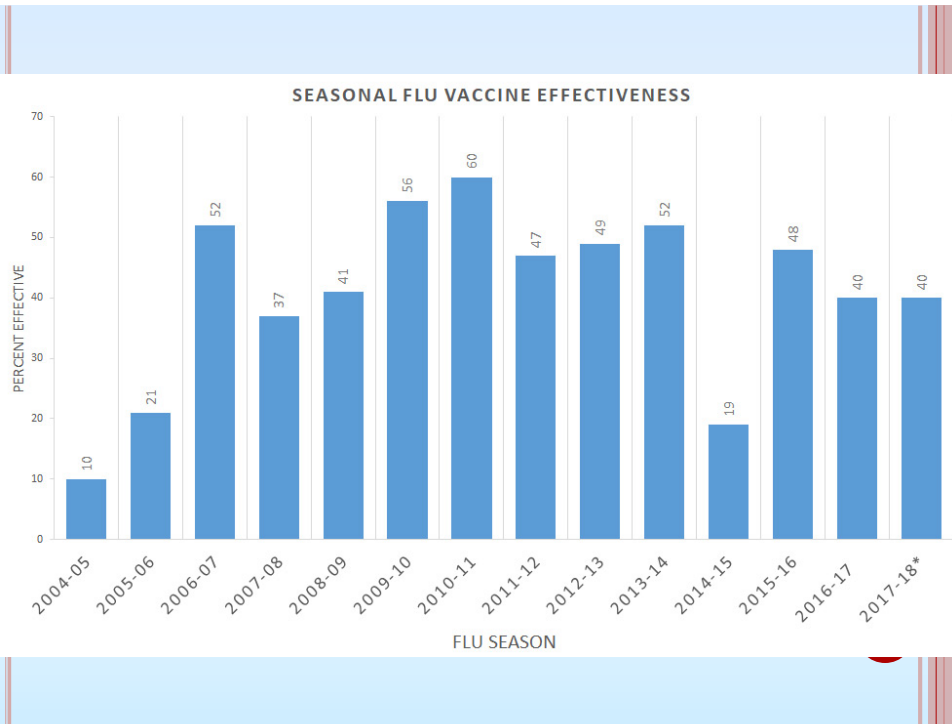


- In advance, hard to know which will circulate: sometimes both lineages



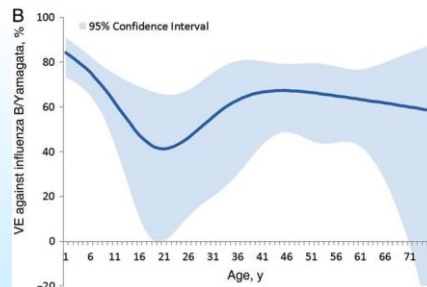
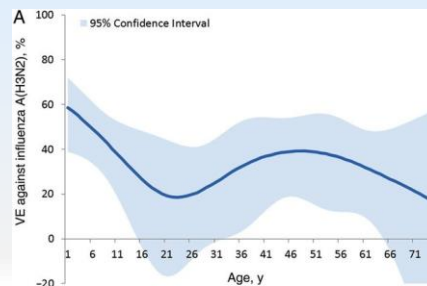
RECOMMENDATION CHANGES FOR 2018-2019

- LAIV again a recommended option
- Most SD egg-based flu shots will be quadrivalent
- All recombinant vaccine will be quadrivalent
- Cell-grown flu vaccine will be quadrivalent
 - A(H3N2) and both B viruses will be cell-derived
 - A(H1N1) will be egg-derived
- No intradermal flu vaccine available
- Changes in age recommendation for two vaccines
 - Previously licensed for ages 18+, Afluria Quadrivalent is now licensed for ages 5+
 - Previously licensed for ages 3+, Fluarix Quadrivalent is now licensed for ages 6m+



WHAT HUMAN FACTORS AFFECT VACCINE EFFECTIVENESS?

- Age
- Prior exposure to flu disease and vaccine
 - Original antigenic sin hypothesis
 - Antigenic distance
- Health conditions
 - Immunocompromise
 - Cancer, dialysis



the benefits of flu vaccination 2016-2017

The estimated number of flu **illnesses prevented** by flu vaccination during the 2016-2017 season:

5.3 million,

about the population of the Atlanta metropolitan area.



The estimated number of flu **medical visits prevented** by vaccination during the 2016-2017 season:

2.6 million,

or more than the number of students in all K-12 schools in Florida.



The estimated number of flu **hospitalizations prevented** by vaccination during the 2016-2017 season:

85,000,

or more than the number of hospital beds in California and Oregon.



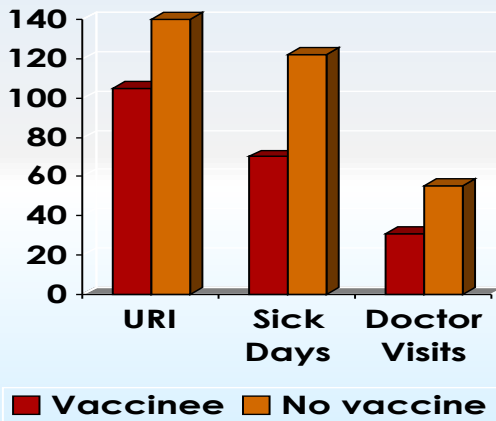
DATA: Influenza Division program impact report 2016-2017, <https://www.cdc.gov/flu/about/disease/2016-17.htm>.

get vaccinated
www.cdc.gov/flu



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

BENEFIT OF IIV IN HEALTHY ADULTS AGED 18-64



○ Saved \$46.85 per person vaccinated

Source: *N Engl J Med.* 1995;333:889-893.

INACTIVATED INFLUENZA VACCINE: ADVERSE EFFECTS

- Placebo-controlled trial
- 20% of vaccinees compared with 5% of placebo recipients had sore arm ($P < .001$)
- No other significant differences

Source: *JAMA*. 1990;264:1140.

ACIP/CDC POLICY CONSIDERATIONS:

- Is the vaccine effective?
- Is the vaccine safe?
- Is the public health impact based on amount of potentially preventable disease sufficient?
- Is it programmatically feasible (e.g., add more injections?)
- Is it cost-effective?
- ACIP uses explicit, evidence-based grading process



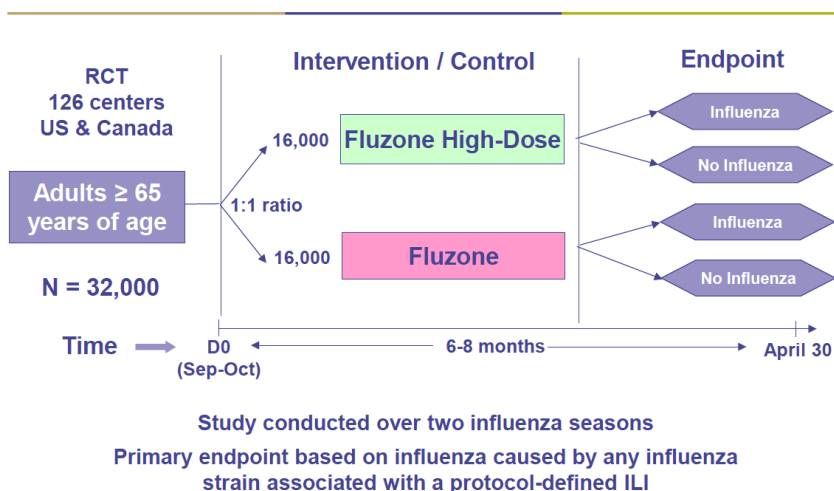
ORIGINAL ARTICLE

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.

ABSTRACT

Trial Design (FIM12)



Benefit Demonstrated Across Influenza Types^a (FIM12)

Type A and B, combined

	Fluzone High-Dose N=15,892 n (%)	Fluzone N=15,911 n (%)	Relative Efficacy % (95% CI)
Associated with PD ILI ^b	227 (1.43)	300 (1.89)	24.2 (9.7; 36.5)

Influenza A

	Fluzone High-Dose N=15,892 n (%)	Fluzone N=15,911 n (%)	Relative Efficacy % (95% CI)
Associated with PD ILI ^b	190 (1.20)	249 (1.56)	23.6 (7.4; 37.1)

Influenza B

	Fluzone High-Dose N=15,892 n (%)	Fluzone N=15,911 n (%)	Relative Efficacy % (95% CI)
Associated with PD ILI ^b	37 (0.23)	51 (0.32)	27.4 (-13.1; 53.8)

^a Laboratory-confirmed influenza regardless of similarity; per-protocol analysis set

^b Protocol-defined influenza-like illness

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Safety Results, Entire Study Period^a (FIM12)

	Fluzone High-Dose (N=15,992)		Fluzone (N=15,991)	
	n	%	n	%
Subjects experiencing at least one:				
SAE	1323	8.27	1442	9.02
Related SAE	3 ^d	0.02	0	0.00
AE of Special Interest (AESI)	3 ^b	0.02	6 ^c	0.04
SAE leading to study discontinuation	99	0.62	103	0.64
Death (any cause)	83	0.52	84	0.53

^a Full analysis set (subjects categorized by vaccine received)

^b AESI: Fluzone High-Dose group: Bell's palsy, acute disseminated encephalomyelitis (ADEM), and Stevens-Johnson Syndrome (Days 53, 117, and 166).

^c AESI: Fluzone group: 5 cases of Bell's palsy (Days 9 through 204) and 1 case of Guillain-Barré Syndrome (Day 95).

^d Related SAEs: Fluzone High-Dose group: left cranial nerve VI palsy (Day 1), hypovolemic shock with diarrhea (Day 1), and ADEM (Day 117).

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ACIP/CDC POLICY CONSIDERATIONS:

- Is the vaccine effective?
- Is the vaccine safe?
- Is the public health impact based on amount of potentially preventable disease sufficient?
- Is it programmatically feasible (e.g., add more injections?)
- Is it cost-effective?
- ACIP uses explicit, evidence-based grading process



ADMINISTRATION OF LAIV

- Spray 0.25 mL into first nostril, take off clip, spray remainder in other nostril

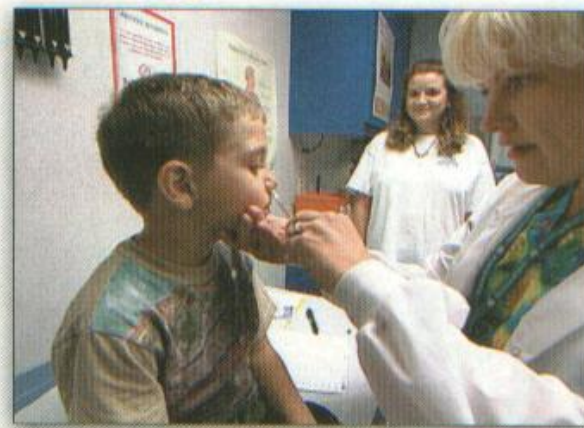


Photo courtesy MedImmune and Wyeth

Evidence Profile—LAIV vs. IIV—2-8-year-olds Lab-confirmed Influenza—Randomized Studies (CRITICAL)

Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect		Quality
					RR [95% CI]	Risk Difference with LAIV [95% CI]	
2	Not serious	Not Serious	Not Serious	Not Serious	0.47 [0.38–0.58]	46 fewer per 1000 [36–54 fewer]	1 (High)

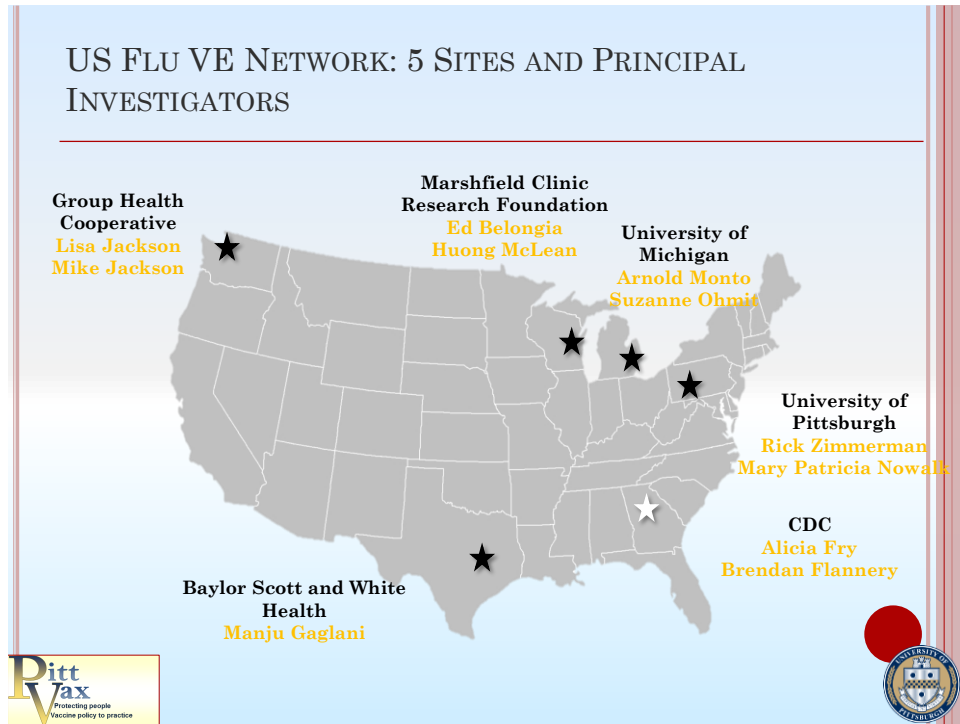
- Data from both studies restricted to children aged ≥ 24 m on this meta-analysis by Ambrose et al, Vaccine 2012)

Study or Subgroup	Experimental		Control		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
Ashkenazi 2006 (24-71M)	23	790	46	819	18.8%	0.52 [0.32, 0.85]	
Belshe 2007 (24-59M)	94	2083	205	2083	81.2%	0.46 [0.36, 0.58]	
Total (95% CI)		2873		2902	100.0%	0.47 [0.38, 0.58]	
Total events	117		251				
Heterogeneity: Tau ² = 0.00; Chi ² = 0.19, df = 1 (P = 0.66); I ² = 0%							
Test for overall effect: Z = 6.96 (P < 0.00001)							

POLICY AND US FLU VE NETWORK

- Based on the Meta-Analyses, CDC decided to prefer LAIV for children 2-8 for 2014-15
- So the US Flu VE Network expanded data collection to see what would happen



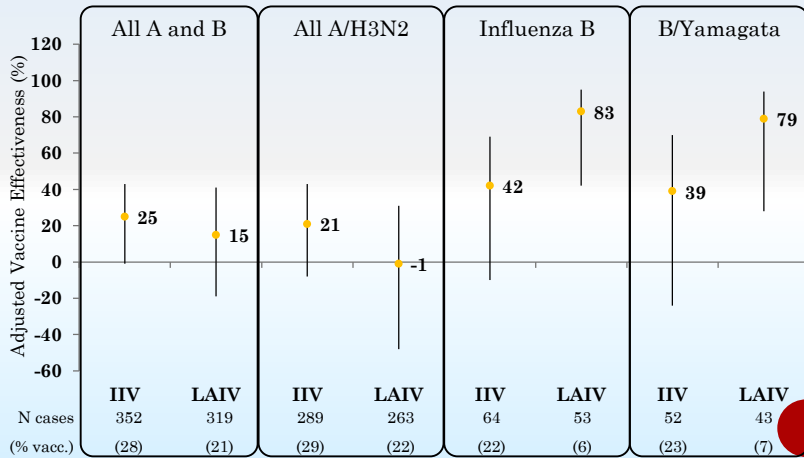


US FLU VE NETWORK METHODS

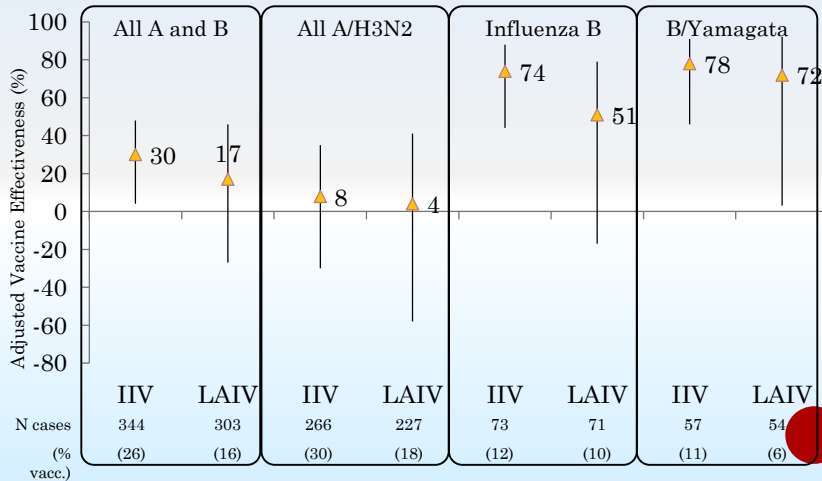
- Test negative case-control study
- Enrollees:
 - Ambulatory patients aged >6 months attending medical facility
 - Acute respiratory illness with cough <7 days duration
- Influenza infection confirmed by CDC's RT-PCR
 - Cases: Influenza PCR-positive
 - Controls: Influenza PCR-negative
 - Vaccination status:
 - Confirmed by medical records and registries at 1 site
 - Plausible self-report and medical records/registries at 4 sites
 - Fully vaccinated at least 14 days prior to illness onset or unvaccinated, excluding partially vaccinated children

Logos for Pitt 7ax and the University of Pittsburgh are visible in the bottom corners.

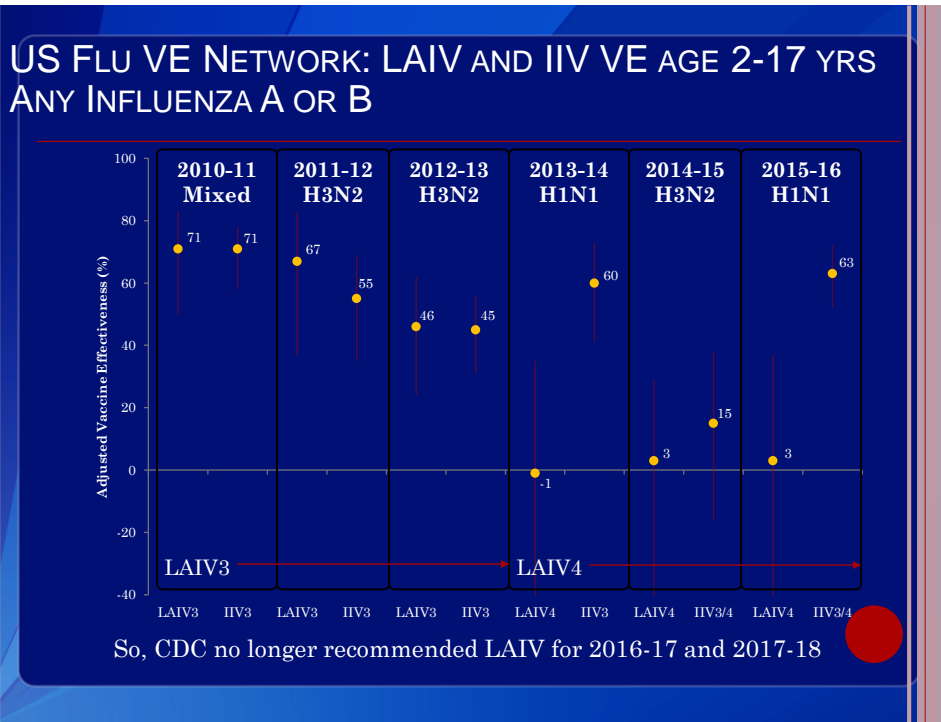
ADJUSTED VE BY INFLUENZA TYPE/SUBTYPE AND VACCINE TYPE FOR FULLY VACCINATED CHILDREN AGES **2-8 YEARS**, US FLU VE NETWORK 2014-2015



ADJUSTED VE BY INFLUENZA TYPE/SUBTYPE AND VACCINE TYPE FOR FULLY VACCINATED CHILDREN **AGES 9-17 YEARS**, US FLU VE NETWORK 2014-2015



So ACIP went back to neutral on LAIV

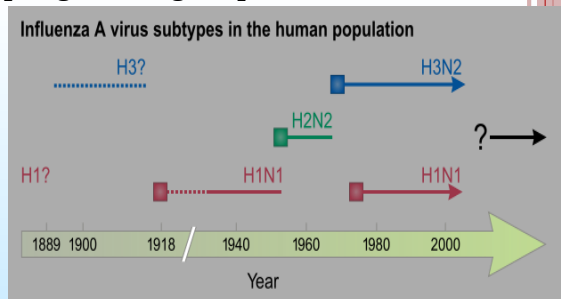


RETURN OF LIVE ATTENUATED INFLUENZA VACCINE (LAIV) AS OPTION FOR 2018-19

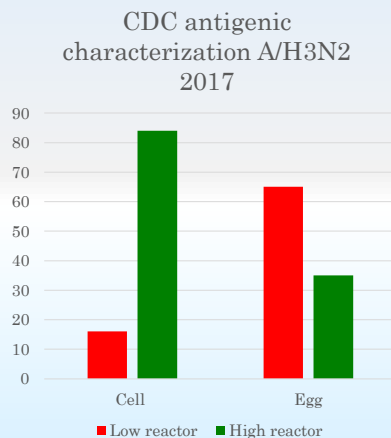
- Manufacturer changed H1N1 construct to replicate better
- Shedding studies presented to CDC show better shedding
 - Therefore should work better
- Feb 2018, ACIP voted to allow the return of LAIV as an option for the Fall of 2018
- Success story:
 - Flu VE Network found a problem
 - ACIP changed recommendations in response
 - Manufacturer made changes to improve the vaccine

H3N2 PROBLEMS

- Highest morbidity and mortality, especially in seniors: Why?
 - Immunosenescence?
 - Birth cohort imprinting – baby boomers and seniors less protected
 - Interference from past vaccinations/infections
- Highest viral mutation rate
- Co-circulation of multiple genetic groups and clades



EGG-BASED ADAPPTIONS?



- Circulating **virus** has a glycosylation site since 2014-15 that can block antibody binding
- Egg-based vaccines lack the glycosylation site due to a T160K mutation to promote vaccine growth in eggs
- Most US vaccine is egg based.
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-virus:
 - Still has the T160K mutation

EGG-FREE OPTIONS

- Cell-based vaccine – limited data until later in 2018
- Recombinant vaccine:

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older

RELATIVE EFFICACY RIV – BETTER IN 9 OF 12

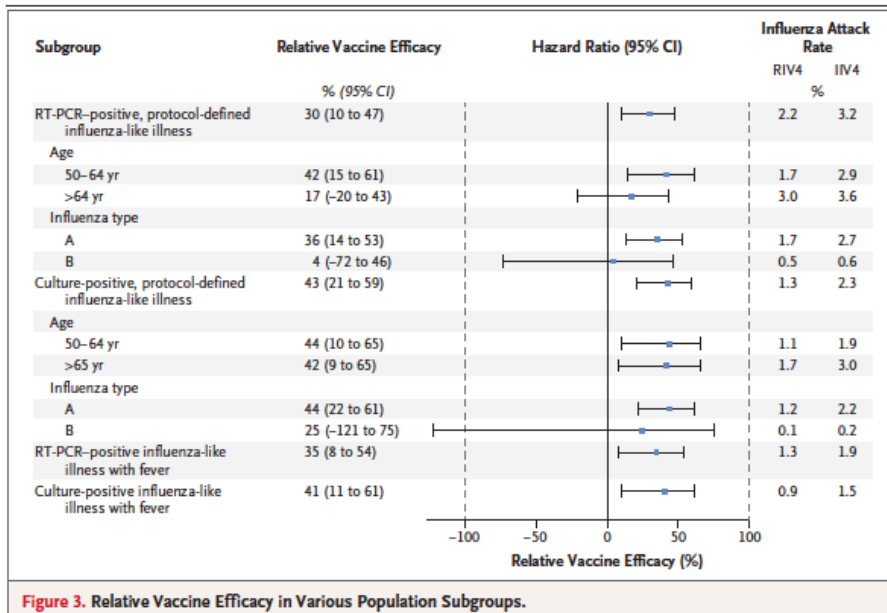


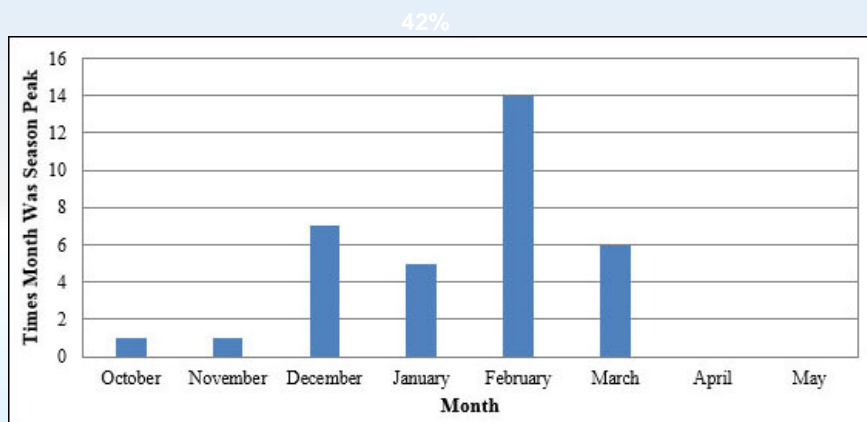
Figure 3. Relative Vaccine Efficacy in Various Population Subgroups.

WHO RECOMMENDED VACCINE COMPOSITION FOR SOUTHERN HEMISPHERE 2019

- Egg Based Trivalent
 - A/Michigan/45/2015 (H1N1)pdm09-like virus;
 - A/Switzerland/8060/2017 (H3N2)-like virus; and
 - B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage)
- Egg Based Quadrivalent
 - Additional a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)
- Non-egg Based vaccines
 - A/Singapore/INFMH-16-0019/2016-like virus for A(A3N2) component



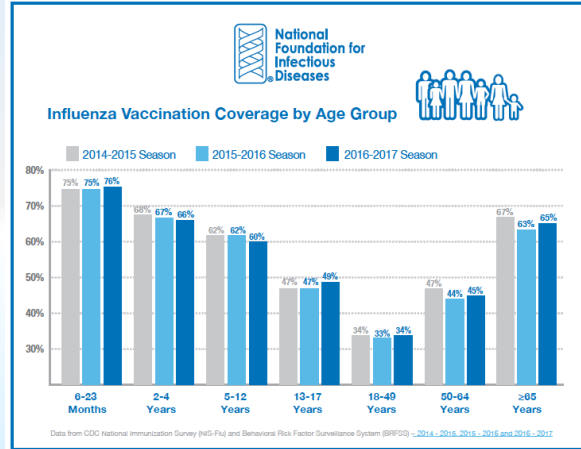
MONTH OF PEAK INFLUENZA ACTIVITY – UNITED STATES, 1982-2016



Network showed some evidence of low level waning

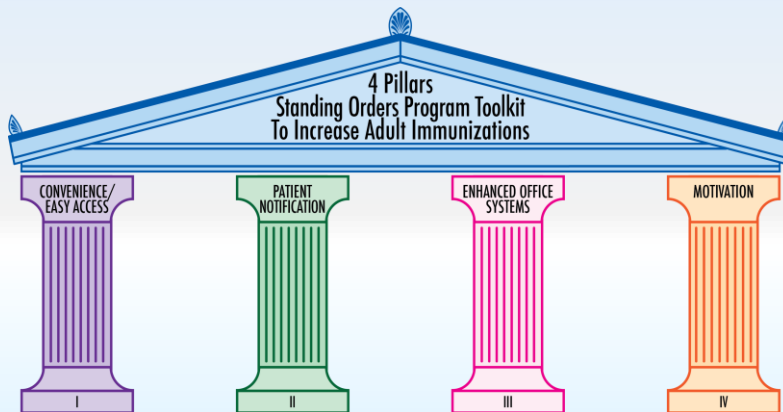


INFLUENZA VACCINATION COVERAGE BY AGE, UNITED STATES



HP2020 Targets: 70% ≥19 years, 90% HCP ≥19 years

4 PILLARS OF SUCCESSFUL VACCINATION PROGRAMS



4pillarstoolkit.pitt.edu



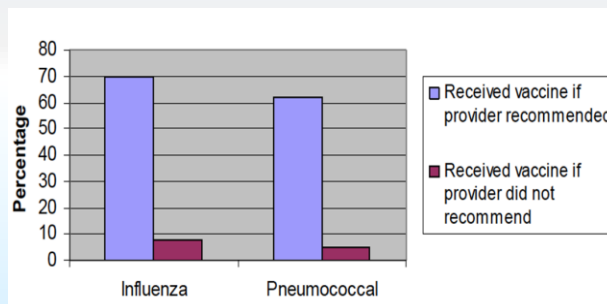
PILLAR 1: CONVENIENT VACCINATION PROGRAMS

- **Extended vaccination season**
 - Starts when influenza vaccine arrives
 - Continues into the influenza disease season for unvaccinated
 - Season unpredictable & some benefit possible
 - 2 waves of influenza may occur
- **Express vaccination services**
 - Vaccination only services:
 - Dedicated evening or weekend vaccine-only services
 - Walk-in vaccination station
 - Nursing vaccination visits



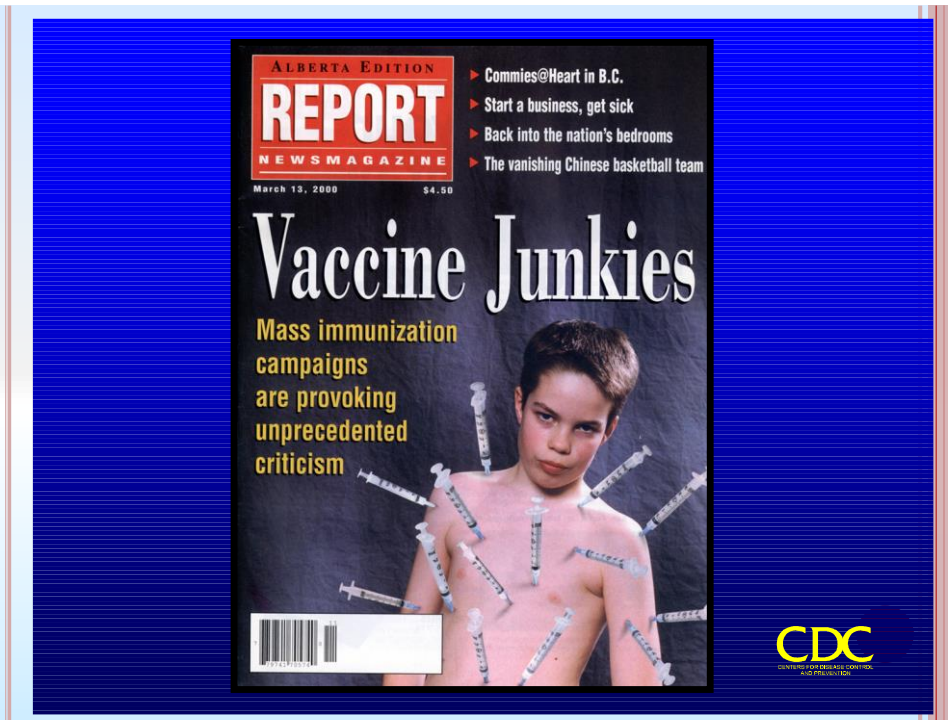
PILLAR 2: PATIENT COMMUNICATION

- Convenient Vaccination Services
- Notification Methods
 - Autodialer; Email/text; Office posters/videos; Answering service “on-hold” messages; Mail
- Physician recommendation is essential



MMWR 1988;37:657-61





PROVIDERS SHOULD DISCUSS SERIOUS NATURE OF VACCINE PREVENTABLE DISEASES



Families Fighting Flu
www.familiesfightingflu.org



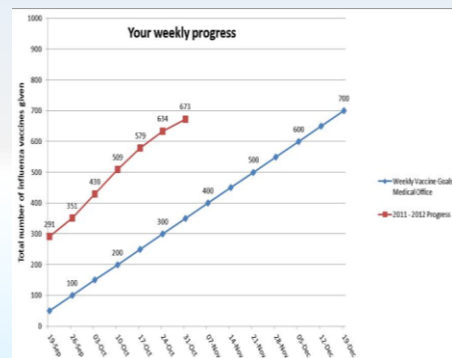
PILLAR 3: ENHANCED OFFICE VACCINATION SYSTEMS

- **Assessment of vaccination as a routine part of the office visit by nursing staff at check-in/rooming:**
 - Prompts in EMR
 - Health maintenance or immunization section review
 - Routinely address “Is vaccination status up to date?” as part of vital signs
- **Empowering staff to vaccinate by standing orders**
- **Combination of assessment and SOPs should reduce missed opportunities**



PILLAR 4: MOTIVATION

- Ongoing motivation is a key to success
 - Set goals for improving rates
 - Identify an **Immunization Champion**
 - Champion monitors weekly progress towards goals
 - Shares progress with team
 - Celebrate achievements
 - Consider rewards



SOP CASE STUDY - URBAN PRACTICE

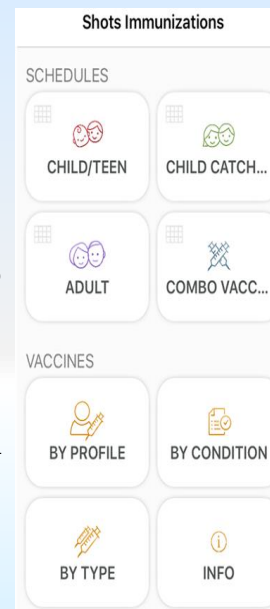
- Effective office manager and lead physician (Immunization Champions)
- Leaders inspired staff to take responsibility for assessing vaccination status and vaccinating patients, using SOPs
- Staff appreciated regular feedback on performance and comparison with other sites
- Staff believed that their performance made the difference vaccination rates

Influenza vaccination rates in one urban practice

Age group	2010 (before 4 pillars toolkit)	2011 (after 4 pillars toolkit)	P value
18-49 years	23%	32%	<.001
49-64 years	35%	46%	<.01
≥65 years	52%	69%	<.001

RESOURCES

- CDC schedules and app
- Shots Immunizations by AAFP /STFM
- Online resources
- Immunization Action Coalition
<http://www.immunize.org/>



REMEMBER THE HERMIT



Questions and Answers

