



INFLUENZA VACCINE 2019-2020

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DISCLOSURES



LIVE WELL
SAN DIEGO

- I have no financial disclosures to make related to this presentation
- My family and I are fully immunized, barely!

OBJECTIVES

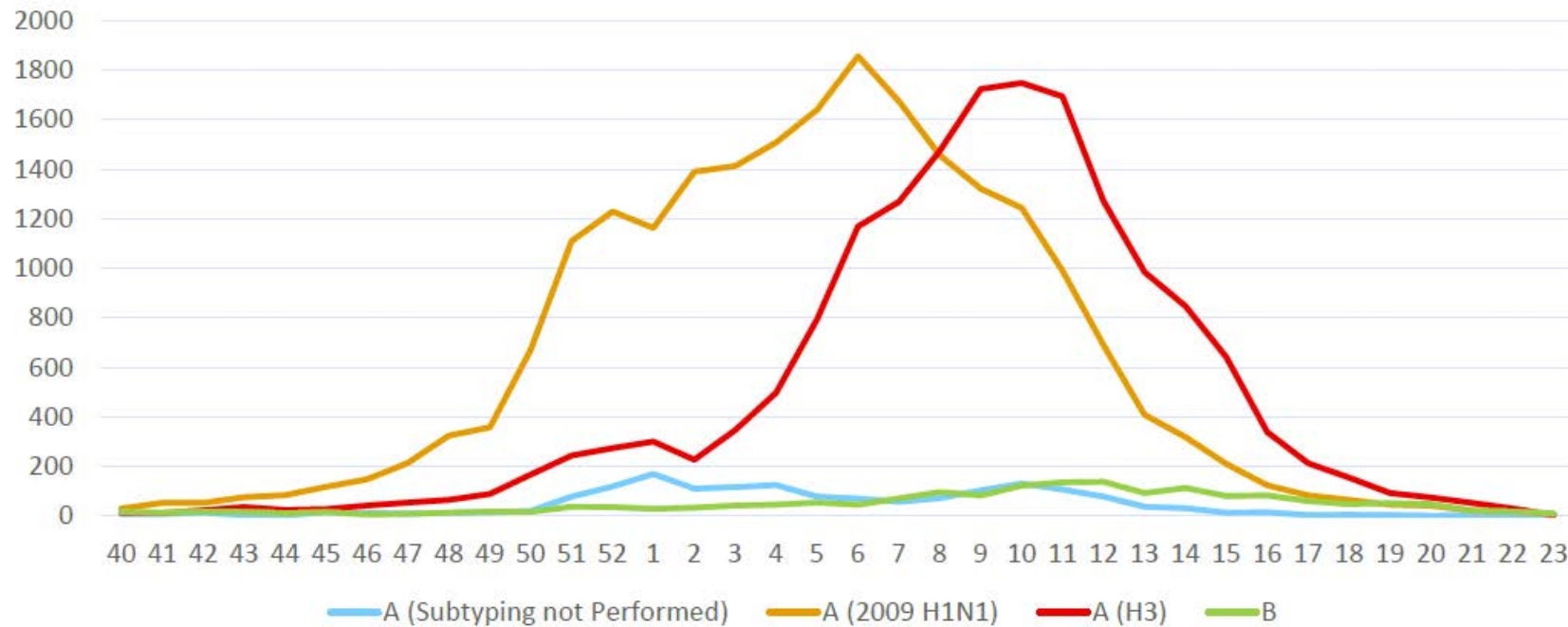


LIVE WELL
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- Explain the names used to describe influenza strains and how variation between influenza strains occurs so that you can track what is happening over time
- Describe how we select the strains that are used for influenza vaccine each year and why influenza vaccine effectiveness varies each year so that you can explain to your patients why the vaccine doesn't always work as well as we would like
- List the new things in this year's CDC Influenza recommendations so that you can use the vaccines correctly
- Explain who is NOT getting an influenza vaccine so that you are on the lookout for them

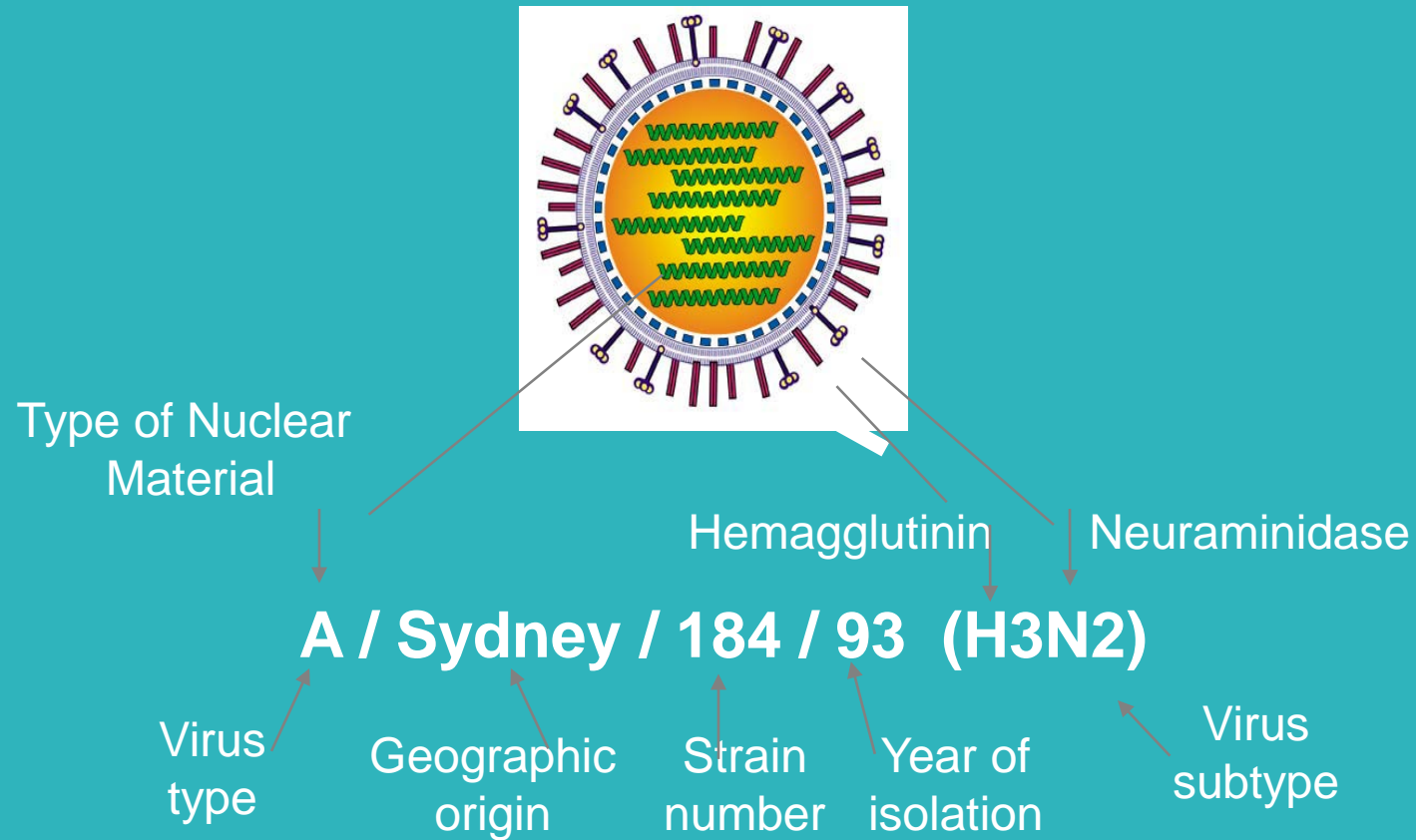


Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, 2018-19 Season



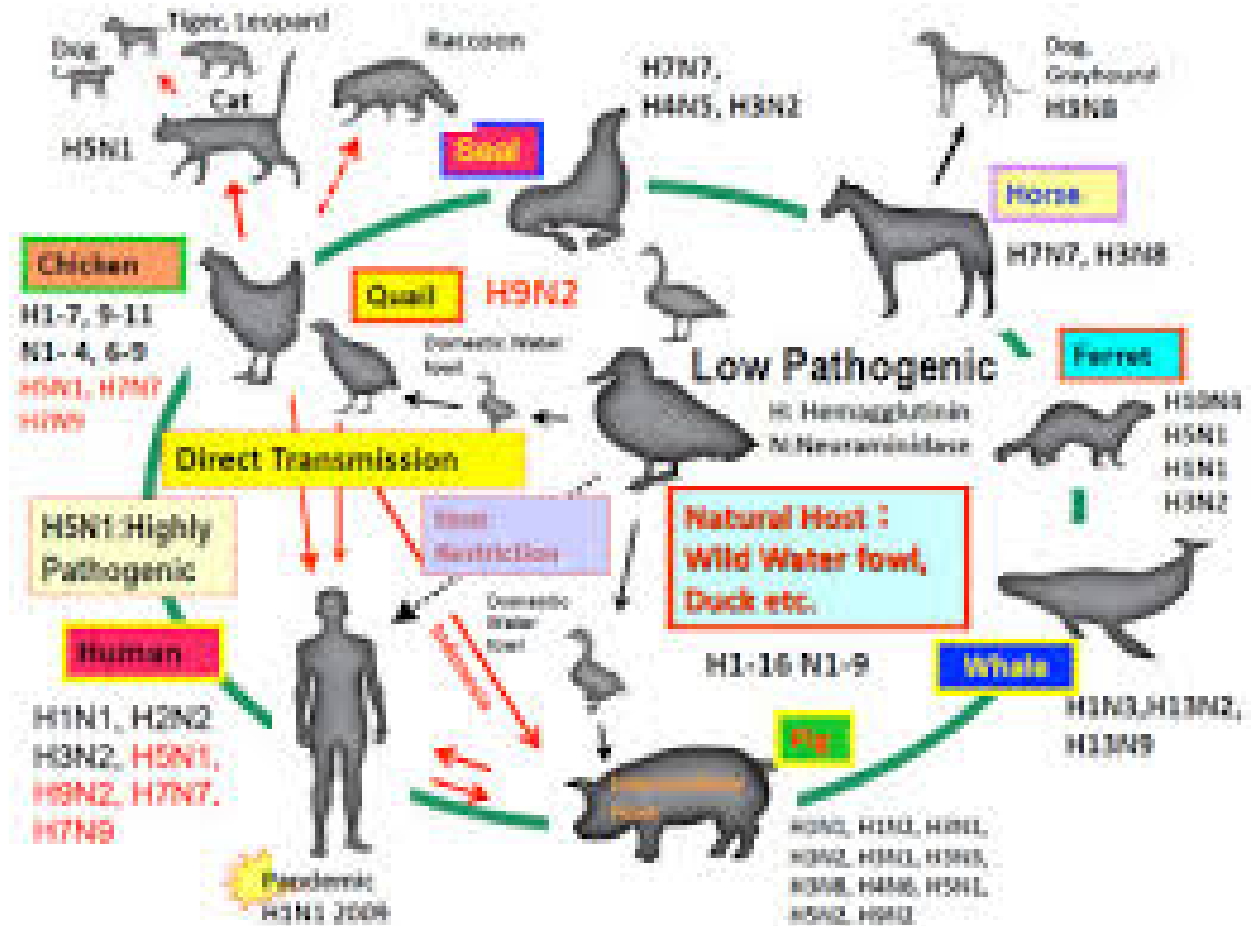
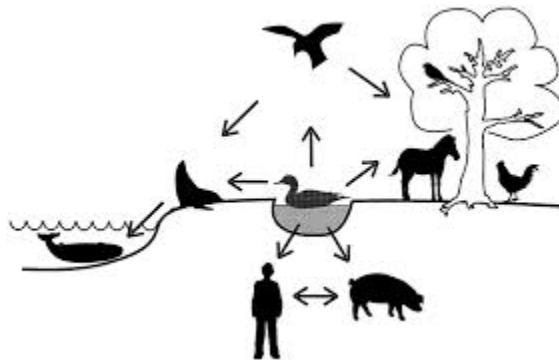
<https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2019-06/flu-2-Brammer-508.pdf>

INFLUENZA VIRUS NOMENCLATURE

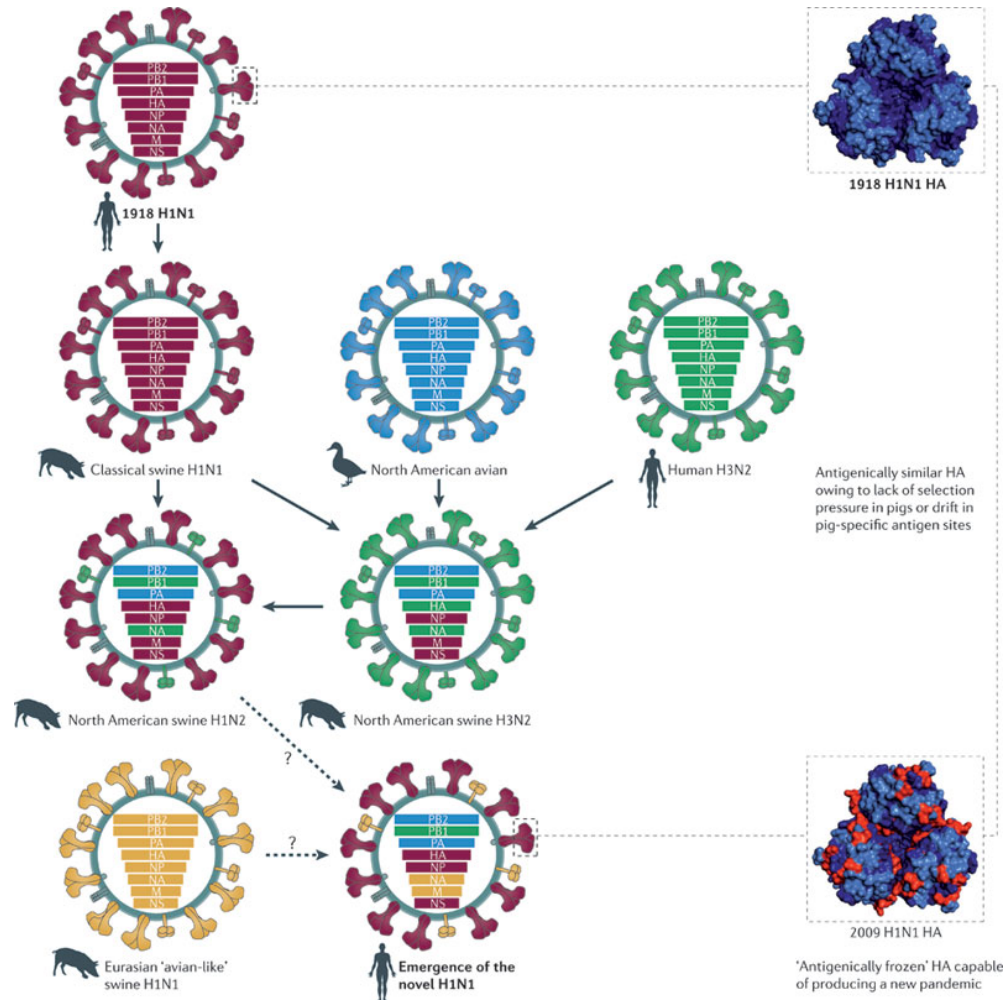


1. CDC. Atkinson W, et al. Chapter 13: Influenza. In: Epidemiology and Prevention of Vaccine-Preventable Diseases, 4th ed. Department of Health and Human Services, Public Health Service, 1998, 220

INFLUENZA ON EARTH



ANTIGENIC SHIFT-TOTALLY NEW STRAINS



- Exchange of segments of RNA create dramatic shifts in the virus
- These are happening all the time in nature
- Occasionally these shifts lead to new strains that easily infect humans and can cause a pandemic

HOW DO WE PICK INFLUENZA VACCINE STRAINS?



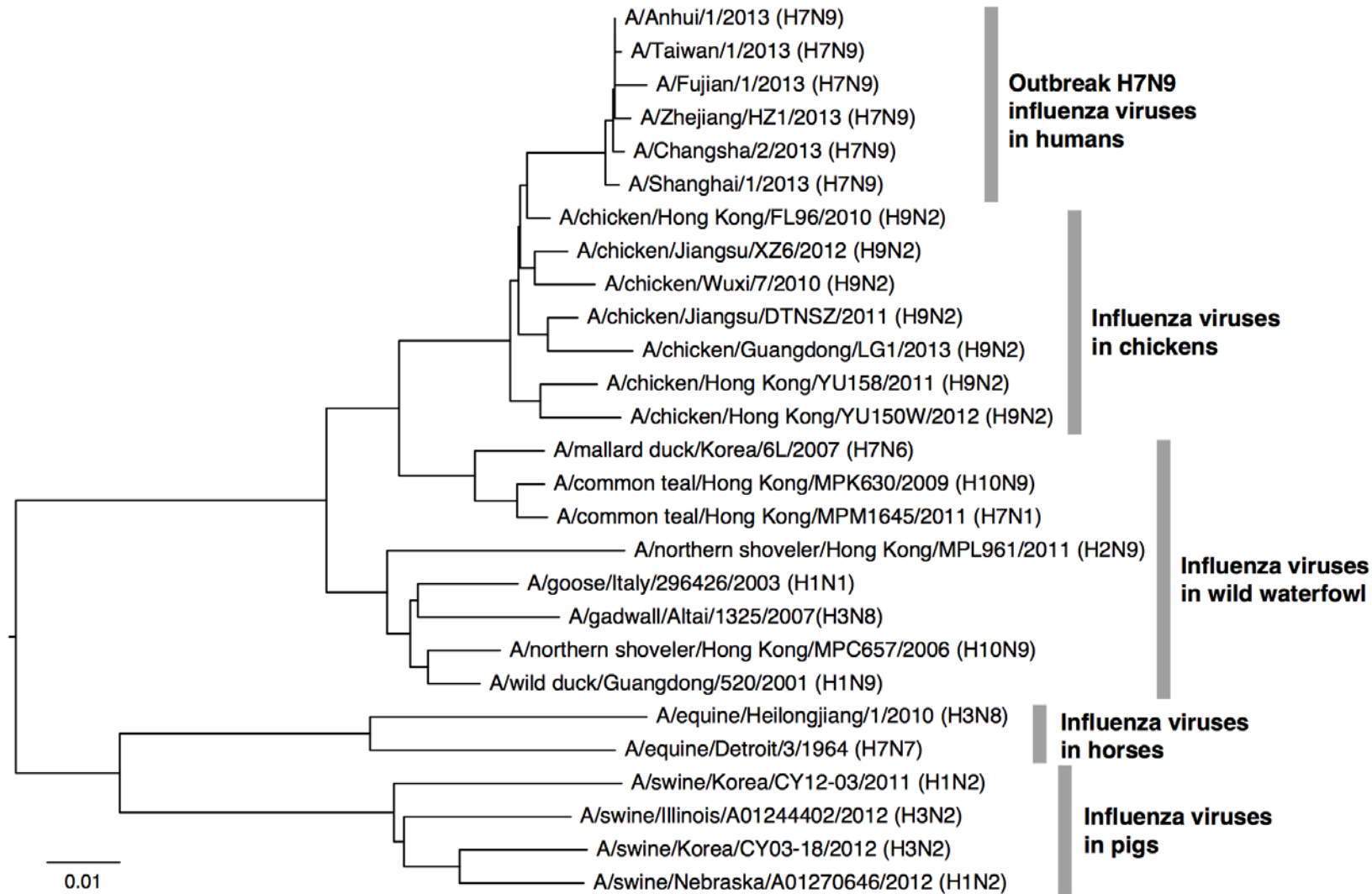
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- Worldwide surveillance
- Sophisticated laboratory analysis
 - Serologic comparisons
 - Nucleic acid sequencing
- WHO expert panel
- FDA VRBPAC-Vaccines and Related Biological Products Advisory Committee

GENETIC COMPARISONS



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The closer
together on the
tree the more
closely related



Seasonal Influenza Vaccine Production Timetable

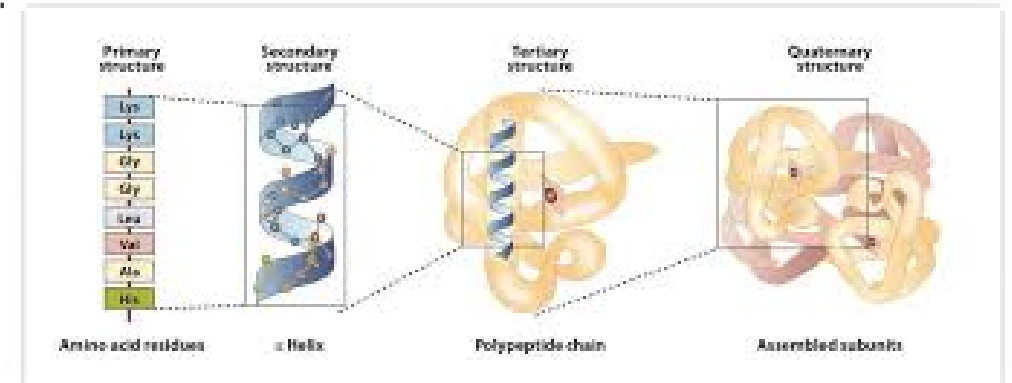
- This slide is to illustrate the production timeframe of seasonal influenza vaccine starting from surveillance to the administration of vaccine to the general public

Steps	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Surveillance												
Select Strains												
Reference Virus												
Reagents												
Production												
Release												
Distribution												
Administer												

WHY DO WE GET IT WRONG?



- We choose the vaccine in February
- Influenza virus is an RNA virus and subject to antigenic **drift**
 - In order for influenza virus to multiply the RNA has to be duplicated by RNA polymerase
 - RNA polymerases are not very accurate
 - RNA sequence: ...AGCUAAGAA... »» ...AGUUAAGAA...
 - Codons: ...AGC-UAA-GAA ...»» ...AGU-UAA-GAA...
 - Amino acids: ...XYZ... »» ...QYZ...
 - Protein: original structure »» drifted structure
 - Immune response: good »» not so good
- Over time the virus changes



VARIATION IN INFLUENZA VACCINE EFFECTIVENESS



Table. Adjusted vaccine effectiveness estimates for influenza seasons from 2005-2016

Influenza Season ¹	Reference	Study Site(s)	No. of Patients ^a	Adjusted Overall VE (%)	95% CI
2004-05	Belongia 2009	WI	762	10	-36, 40
2005-06	Belongia 2009	WI	346	21	-52, 59
2006-07	Belongia 2009	WI	871	52	22, 70
2007-08	Belongia 2011	WI	1914	37	22, 49
2009-10	Griffin 2011	WI, MI, NY, TN	6757	56	23, 75
2010-11	Treanor 2011	WI, MI, NY, TN	4757	60	53, 66
2011-12	Ohmit 2014	WI, MI, PA, TX, WA	4771	47	36, 56
2012-13	McLean 2014	WI, MI, PA, TX, WA	6452	49	43, 55
2013-14	Unpublished	WI, MI, PA, TX, WA	5990	51	43, 58
2014-15	ACIP presentation, Flannery	WI, MI, PA, TX, WA	9329	23	14, 31
2015-16*	ACIP presentation, Flannery	WI, MI, PA, TX, WA	7563	47*	39, 53*

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

*Estimate from Nov 2, 2015 - April 15, 2016

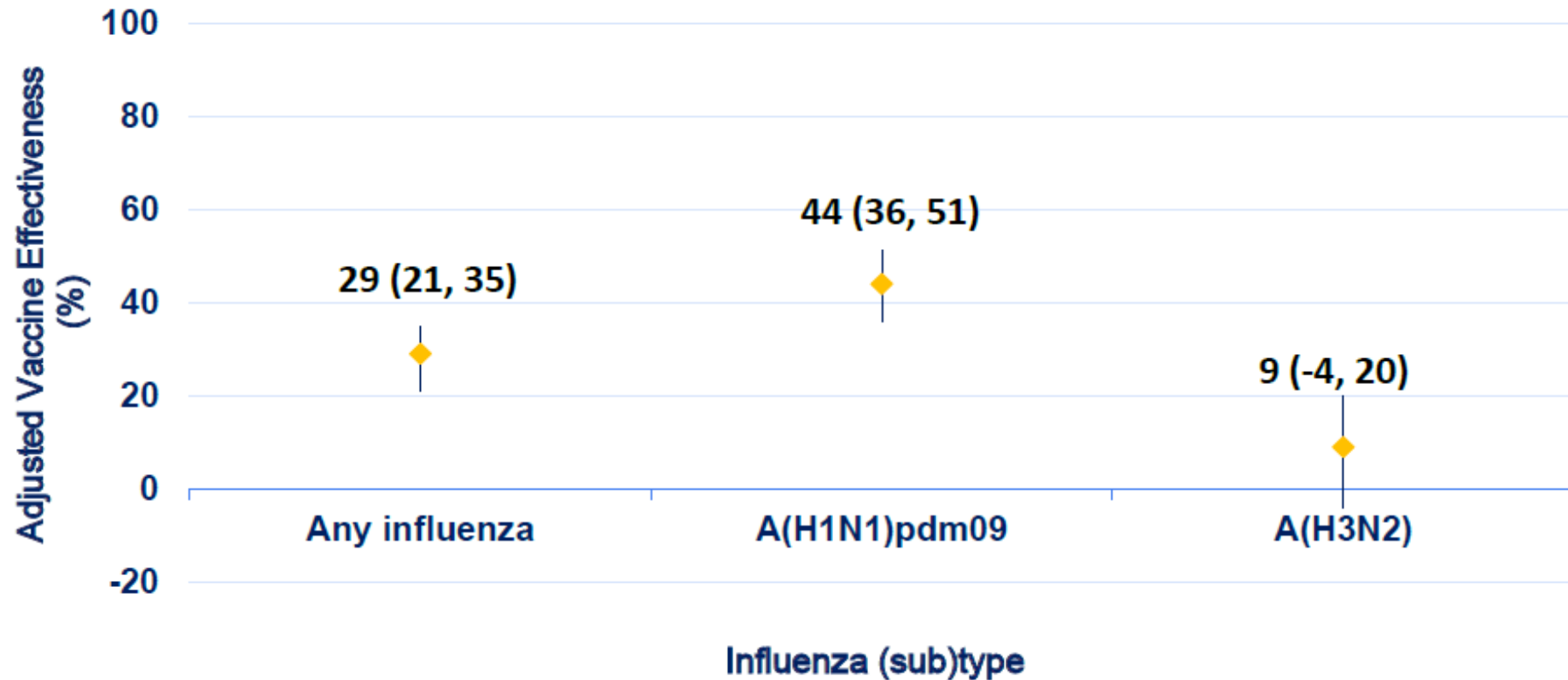
2018-2019 INFLUENZA SEASON

Adjusted vaccine effectiveness against medically attended influenza by age group, US Flu VE Network, 2018–19

	Influenza positive		Influenza negative		Vaccine Effectiveness			
					Unadjusted		Adjusted*	
Any influenza A or B virus	N vaccinated /Total	(%)	N vaccinated /Total	(%)	VE %	95% CI	VE %	95% CI
Overall	1333/2795	48	4059/7246	56	28	(21 to 34)	29	(21 to 35)
Age group (yrs)								
6 mos–8	303/759	40	977/1675	58	53	(43 to 60)	49	(38 to 58)
9–17	221/493	45	319/772	41	-15	(-45 to 8)	6	(-22 to 27)
18–49	323/831	39	1074/2435	44	19	(5 to 31)	25	(10 to 37)
50–64	271/448	60	827/1324	62	8	(-15 to 26)	12	(-12 to 31)
≥65	215/264	81	862/1040	83	9	(-29 to 36)	12	(-29 to 41)

* Multivariable logistic regression models adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrollment, and calendar time.

Adjusted vaccine effectiveness* against medically attended influenza by virus subtype, US Flu VE Network, 2018–19



* Multivariable logistic regression models adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrollment, and calendar time.



Summary

- Overall VE was ~30% against influenza illness and hospitalizations.
 - Vaccine likely prevented between ~40,000 to 90,000 hospitalizations based on previous seasons' estimates
- Vaccine reduced A(H1N1)pdm09- associated outpatient influenza illness by 44% and hospitalizations by 48%-60%
- No significant protection against H3N2 illnesses likely due to emergence of antigenically different A(H3N2) clade 3C.3a
 - WHO has updated the A(H3N2) component of 2019-2020 Northern Hemisphere influenza vaccines
- These VE estimates are preliminary and will be updated when final data are available



LIVE WELL
SAN DIEGO

Can you give the influenza vaccine
too early?



Table 4. Summary of Findings

Outcome	Participants, No. (Studies)	Studies, No.	Evidence Certainty ^a	Δ VE (95% CI)	VE (95% CI), by Time After Vaccination	
					15–90 d	91–180 d
Influenza A(H3)	10 736 cases, 27 689 controls	11	Moderate	-33 (-57 to -12)	45 (34 to 54)	13 (-10 to 31)
Influenza B	6424 cases, 17 877 controls	6	Low	-19 (-33 to -6)	62 (52 to 70)	43 (33 to 52)
Influenza A(H1)	5148 cases, 17 044 controls	5	Low	-8 (-27 to 21)	62 (35 to 78)	54 (43 to 63)

Aggregate odds ratios from the meta-analysis in [Figure 2](#) were converted to VE values, stratified by influenza virus type/subtype and time since vaccination, with bootstrapped estimates used for Δ VE.

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

^aBased on the Grading of Recommendations Assessment, Development and Evaluation.

WHEN TO GIVE INFLUENZA VACCINE



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- The goal is to immunize everyone by November 1
- Immunize children who need 2 doses of vaccine as soon as you can
- Immunize anyone who may not be back/come back by November 1
- Otherwise wait until September
- No recommendation for a second dose half way through the season

INFLUENZA-WHO DO WE WORRY ABOUT THE MOST?



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■ HIGH RISK CONDITIONS

- Children under 5 years
- Pregnant women
- Adults over 50 years
- Everyone with chronic lung, heart, kidney, liver, neurologic diseases
- Residents of long-term care facilities
- Immunocompromised people
- American Indian/Alaskan Natives
- Persons with extreme obesity
- Children on chronic aspirin

WHO ELSE IS VERY IMPORTANT TO IMMUNIZE?



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- People who care for the high risk groups
 - Household contacts
 - Other caregivers
- Health care personnel



2019-20 Primary Updates: Vaccine Composition

■ Trivalent Vaccines

- A/Brisbane/02/2018 (H1N1)pdm09-like virus—*updated*
- A/Kansas/14/2017 (H3N2)-like virus—*updated**
- B/Colorado/06/2017-like virus (Victoria lineage)

■ Quadrivalent Vaccines

- Above three, plus B/Phuket/3073/2013-like virus (Yamagata lineage)

** Selection of H3N2 component delayed until March 21, 2019*

INFLUENZA UPDATE AND ACIP LANGUAGE ABOUT WHEN TO VACCINATE



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2018-2019 season was “moderate” but with a late surge of influenza A H3N2 strains that did not match the vaccine components

New influenza A H3N2 and H1N1 strains in the 2019-2020 vaccine

New language: for those who only require 1 dose of vaccine (everyone except children under 9 years of age) don’t give vaccine before September

Consider not giving novel adjuvanted vaccines (Shingrix, Heplisav, Flud) on the same day



Influenza vaccine abbreviations¹

Abbreviation	Vaccine
IIV3, IIV4	Trivalent and quadrivalent inactivated influenza vaccine
IIV3-HD	High-dose trivalent inactivated influenza vaccine (approved for use in individuals 65+ years old)
ccIIV4	Cell culture-based quadrivalent inactivated influenza vaccine
RIV4	Recombinant quadrivalent influenza vaccine
aIIV3	Adjuvanted trivalent inactivated influenza vaccine (approved for use in individuals 65+ years old)
LAIV4	Quadrivalent live attenuated influenza vaccine

2019-2020 INFLUENZA VACCINE PRODUCTS



TABLE 1. Influenza vaccines — United States, 2019–20 influenza season*

Trade name (Manufacturer)	Presentation	Age indication	HA (IIVs and RIV4) or virus count (LAIV4) for each vaccine virus (per dose)	Route	Mercury (from thimerosal) (µg/0.5mL)
IIV4—Standard Dose—Egg based†					
Afluria Quadrivalent (Seqirus)	0.25-mL PFS [§]	6 through 35 mos	7.5 µg/0.25 mL [§]	IM [¶]	—
	0.5-mL PFS [§]	≥3 yrs	15 µg/0.5 mL [§]		—
	5.0-mL MDV [§]	≥6 mos (needle/syringe) 18 through 64 yrs (jet injector)			24.5
Fluarix Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM [¶]	—
FluLaval Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM [¶]	—
	5.0-mL MDV	≥6 mos			<25
Fluzone Quadrivalent (Sanofi Pasteur)	0.25-mL PFS**	6 through 35 mos	7.5 µg/0.25 mL**	IM [¶]	—
	0.5-mL PFS**	≥6 mos	15 µg/0.5 mL**		—
	0.5-mL SDV**	≥6 mos			—
	5.0-mL MDV**	≥6 mos			25
IIV4—Standard Dose—Cell culture based (ccIIV4)					
Flucelvax Quadrivalent (Seqirus)	0.5-mL PFS	≥4 yrs	15 µg/0.5 mL	IM [¶]	—
	5.0-mL MDV	≥4 yrs			25
IIV3—High Dose—Egg based† (HD-IIV3)					
Fluzone High-Dose (Sanofi Pasteur)	0.5-mL PFS	≥65 yrs	60 µg/0.5 mL	IM [¶]	—
IIV3—Standard Dose—Egg based† with MF59 adjuvant (aIIV3)					
Fluad (Seqirus)	0.5-mL PFS	≥65 yrs	15 µg/0.5 mL	IM [¶]	—
RIV4—Recombinant HA					
Flublok Quadrivalent (Sanofi Pasteur)	0.5-mL PFS	≥18 yrs	45 µg/0.5 mL	IM [¶]	—
LAIV4—Egg based†					
FluMist Quadrivalent (AstraZeneca)	0.2-mL prefilled single-use intranasal sprayer	2 through 49 yrs	10 ^{6.5–7.5} fluorescent focus units/0.2 mL	NAS	—

Lots of products available
Different types of vaccine
Different presentations
Different ages



TABLE 3. Dose volumes for inactivated influenza vaccines licensed for children aged 6 through 35 months*— United States, 2019–20 influenza season

Trade name (Manufacturer)	Dose volume for children aged 6 through 35 mos (µg HA per vaccine virus)
Afluria Quadrivalent (Seqirus)	0.25 mL (7.5 µg)
Fluarix Quadrivalent (GlaxoSmithKline)	0.5 mL (15 µg)
FluLaval Quadrivalent (GlaxoSmithKline)	0.5 mL (15 µg)
Fluzone Quadrivalent [†] (Sanofi Pasteur)	0.25 mL (7.5 µg) or 0.5 mL (15 µg)

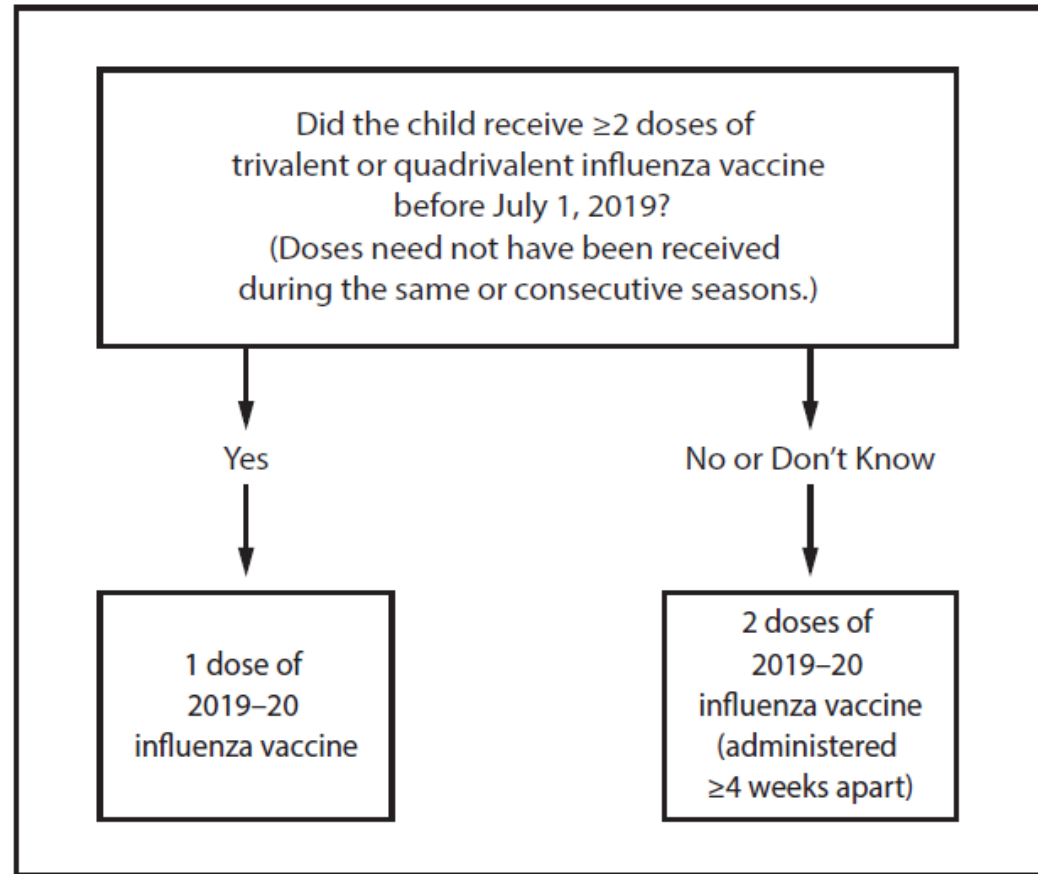
CDC, MMWR August 23, 2019; 68(3)

TWO DOSES OF INFLUENZA VACCINE FOR YOUNG CHILDREN-UPDATE



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FIGURE. Influenza vaccine dosing algorithm for children aged 6 months through 8 years* — Advisory Committee on Immunization Practices, United States, 2019–20 influenza season



One dose of vaccine in this population provides very little protection

* For children aged 8 years who require 2 doses of vaccine, both doses should be administered even if the child turns age 9 years between receipt of dose 1 and dose 2.

CDC, MMWR August 23, 2019; 68(3)

VACCINES FOR OLDER (≥ 65 YEARS) ADULTS



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- High dose IIV3 (HD-IIV3)
- Recombinant IIV4 (RIV)
- Adjuvanted IIV3 (aIIV3)
- Probably all work better than other IIV vaccines
 - HD-IIV3 24% more effective
 - RIV 17-30% more effective
 - aIIV3 ??63% more effective

No preference for these vaccines stated by CDC

CDC, MMWR August 23, 2019; 68(3)



VACCINES

- Influenza-Fluad
- Zoster-Shingrix
- Hepatitis B-Heplisav B

CHARACTERISTICS

- Better immune response
- Lead to higher antibody levels, particularly in adults 65 years of age and older
- Have increased local side effects
 - Sore arm
 - Redness at the injection site
- Have increased systemic side effects
 - Fever
 - Headache
 - Body aches

PEDIATRIC/ADULT INFLUENZA VACCINE 2019-2020

6–35 MONTHS OLD



Afluria® Quadrivalent
Seqirus
0.25 mL single-dose syringe



Fluzone® Quadrivalent
Sanofi Pasteur, Inc.
0.25 mL single-dose syringe



DOUBLE-CHECK THE DOSE!

	6–35 months	3+ years
Afluria® syringes	0.25mL	0.5mL
Fluzone® syringes	0.25mL or 0.5mL	0.5mL
FluLaval® syringes	0.5mL	0.5mL
Fluarix® syringes	0.5mL	0.5mL

Administer the entire dose to appropriate age—do not split 0.5mL dose for multiple uses.

6 MONTHS & OLDER



Fluarix® Quadrivalent
GlaxoSmithKline Biologicals
0.5 mL single-dose syringe



Fluzone® Quadrivalent
Sanofi Pasteur, Inc.
0.5 mL single-dose syringe



FluLaval® Quadrivalent
GlaxoSmithKline Biologicals
0.5 mL single-dose syringe



Fluzone® Quadrivalent
Sanofi Pasteur, Inc.
0.5 mL single-dose vial



Available from CDPH EZIZ web site

<http://eziz.org/assets/docs/IMM-859.pdf>

3 YEARS & OLDER



Afluria® Quadrivalent
Seqirus
5.0 mL** multi-dose vial



FluLaval® Quadrivalent
GlaxoSmithKline Biologicals
5.0 mL** multi-dose vial



Afluria® Quadrivalent
Seqirus
0.5 mL single-dose syringe



Fluzone® Quadrivalent
Sanofi Pasteur, Inc.
5.0 mL** multi-dose vial



4 YEARS & OLDER



Fluceivax® Quadrivalent
Seqirus
0.5 mL single-dose syringe



Fluceivax® Quadrivalent
Seqirus
5.0 mL** multi-dose vial



2–49 YEARS OLD & HEALTHY



FluMist® Quadrivalent
MedImmune Vaccines, Inc.
0.2 mL single-dose nasal sprayer



65 YEARS & OLDER



FLUAD™ Adjuvanted Trivalent
Seqirus
0.5 mL single-dose syringe



18 YEARS & OLDER



FluBlok® Quadrivalent
Protein Sciences
0.5 mL single-dose syringe



Fluzone® High-Dose Trivalent
Sanofi Pasteur, Inc.
0.5 mL single-dose syringe



STORE ALL INFLUENZA VACCINES IN THE REFRIGERATOR.

VFC Questions:
Call 877-2GET-VFC
(877-243-8832)

** Multi-dose vials contain preservative and typically cannot be given to children younger than 3 years of age and pregnant women per California law (Health and Safety Code 124172).

Children under 9 years of age with a history of <2 doses of influenza vaccine are recommended to receive 2 doses this flu season. See bit.do/fluexACIP

Vaccines with the VFC logo are available through the Vaccines for Children Program in 2019-2020 and can only be used for VFC eligible children (≤18 years of age).



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SAN DIEGO**

INFLUENZA VACCINES

HOW DO YOU KEEP THEM STRAIGHT?



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- Is it trivalent or quadrivalent?
- Is it injectable or nasal?
- Is it made in eggs or in cell culture?
- Is it a special product?
- What are its age restrictions?
- Who makes it/brand name?

IS IT TRIVALENT OR QUADRIVALENT?



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- All regular dose IIV this year is quadrivalent
- Some products only available as trivalent
- CDC expresses no preference between trivalent and quadrivalent

IS IT MADE IN EGGS?



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- All are except FluBlok/Protein Sciences Corp and Flucelvax/Novartis
- Flublok is a recombinant vaccine (like Hep B vaccine) and may be referred to as RIV
- Flucelvax is a whole virus vaccine but made in cells and may be referred to as cclIV

IS IT A SPECIAL PRODUCT?



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- IIV High dose-Fluzone High Dose/Sanofi
 - Recommended for those 65 years of age and over
- IIV adjuvanted-Fluad/Seqirus-
 - Recommended for those 65 years of age and over

WHO SHOULD GET A FLU VACCINE?



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- Everyone 6 months of age and older!

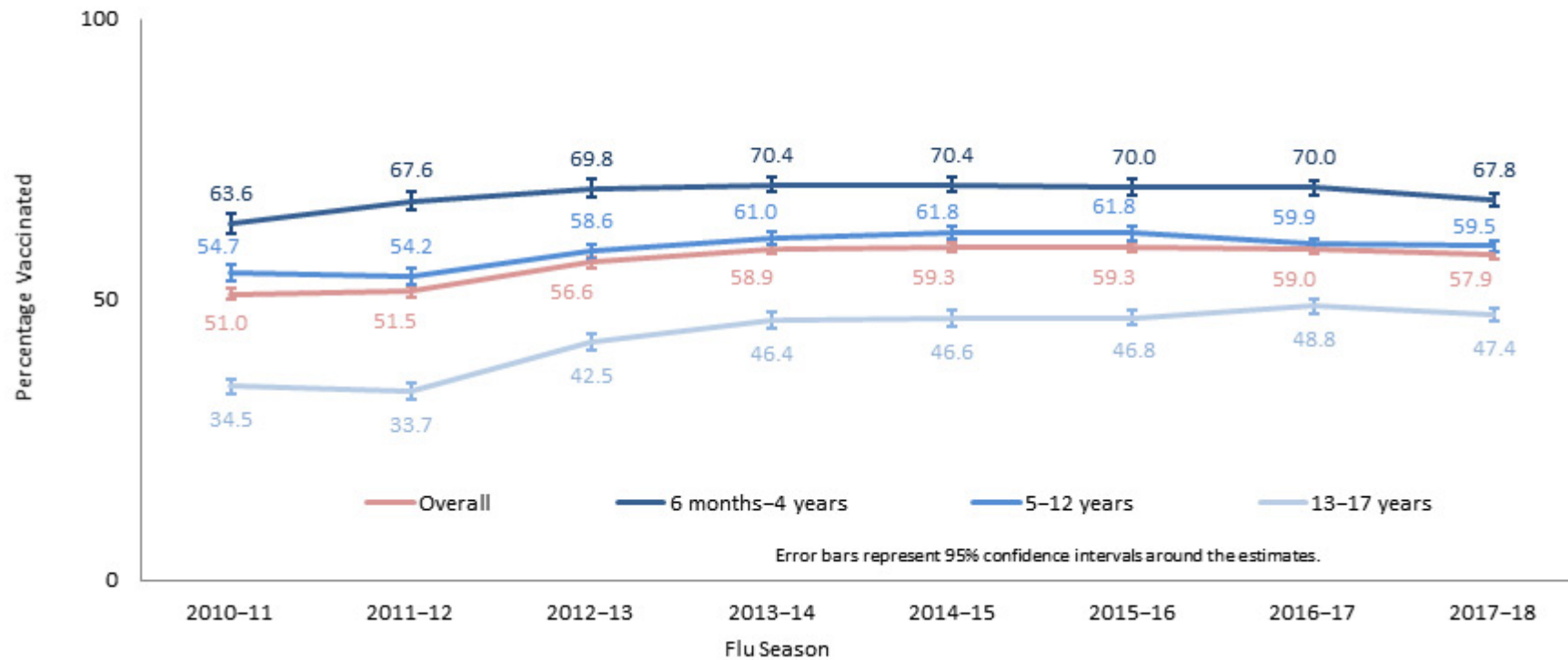


INFLUENZA VACCINE COVERAGE-CHILDREN



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

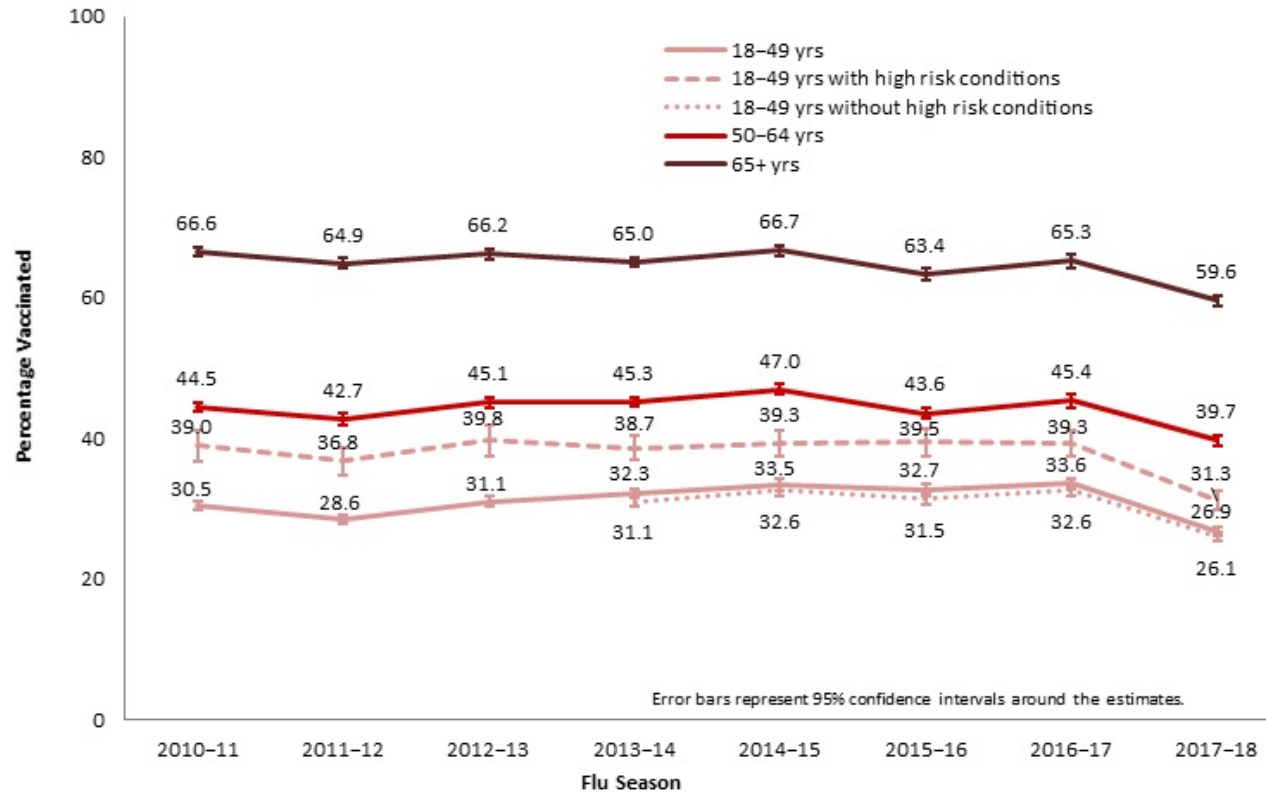


<https://www.cdc.gov/flu/fluview/coversage-1718estimates-children.htm>

INFLUENZA VACCINE COVERAGE -ADULTS



Figure 2. Flu Vaccination Coverage Among Adults, by Age Group and Season, United States, 2010–2018



<https://www.cdc.gov/flu/fluview/covage-1718estimates.htm>



How do we know if
influenza vaccine is
safe?



Vaccine Adverse Event Reporting System (VAERS)

Strengths

- National data
- Accepts reports from anyone
- Rapidly detects safety signals
- Can detect rare adverse events
- Data available to public

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Generally cannot assess causality

- VAERS accepts all reports from all reporters without making judgments on causality, irrespective of clinical seriousness
- As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems



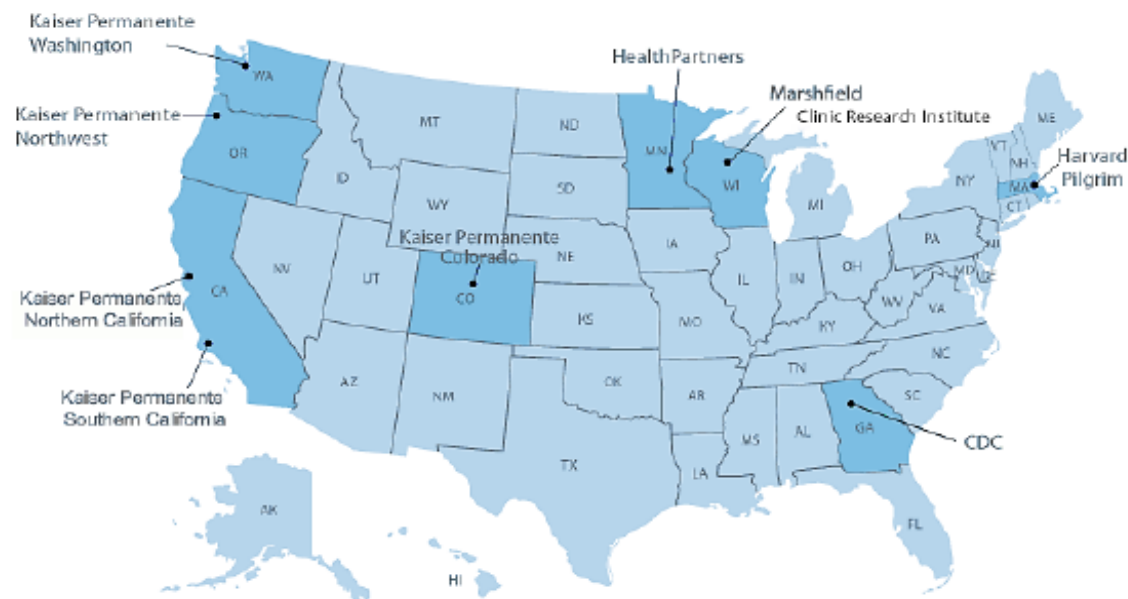
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VSD



Vaccine
Safety
Datalink



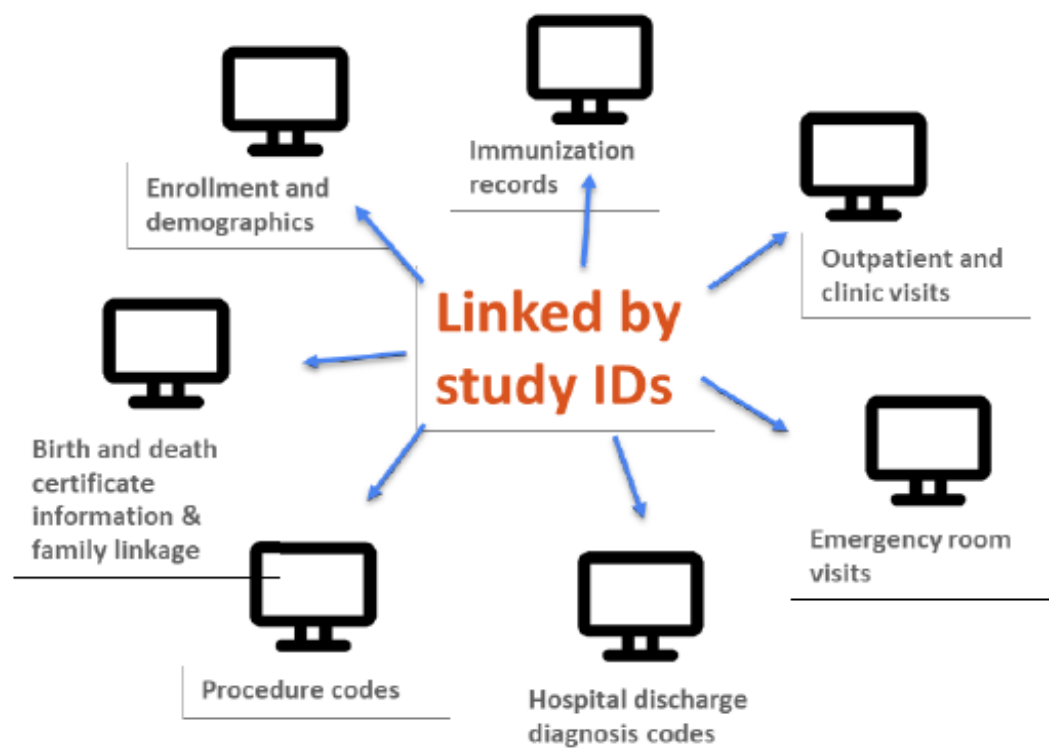
8 participating integrated
healthcare organizations

Shimabukuro, June 2019 ACIP Meeting



LIVE WELL
SAN DIEGO

VSD electronic files + chart review



+



Images created by Wilson Joseph, Meagan Mitchell, Ananth, and Lisa from the noun project

Shimabukuro, June 2019 ACIP Meeting



- Guillain Barre Syndrome-possible risk in line with what has been seen in many prior years with influenza vaccine (e.g.1: 1,000,000 doses)
- ? Of 3 fold increased risk of Bell's Palsy in 4-17 year olds
- Febrile seizures in children under 5 years of age
 - Risk lower than that known for MMR or PCV13 vaccines

INFLUENZA VACCINE AND EGG ALLERGY



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- People who have had an allergic reaction to influenza vaccine should not receive further doses
- Egg allergic people can receive any influenza product that is otherwise appropriate
- Any influenza vaccine product can be given to egg allergic individuals- including those who have had anaphylaxis to egg. You should be just as prepared to treat an anaphylactic reaction to influenza vaccine as you are for any other vaccine
- Observe for 15 minutes after administration
- People have had anaphylaxis should be immunized in a setting that can immediately manage reactions (not a drive by event in a parking lot!)

WHERE TO GO FOR MORE INFORMATION



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- San Diego HHSA Immunization Branch (SDIZ.org)
- California Department of Public Health (www.cdph.ca.gov)
- CDC (cdc.gov/vaccines)