The Flu Stops Here: Enabling Pharmacists and Pharmacy Technicians to Join the Fight

ICHP Annual Meeting
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Oakbrook Terrace, Illinois

Speakers

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Disclosures

- Michael Hogue discloses that he is on the speakers bureau for Pfizer, Inc., and has served as a consultant to GlaxoSmithKline and Sanofi Pasteur. Dr. Hogue has a research grant from Merck & Co., Inc.
- Dennis Williams discloses that his spouse is employed by GlaxoSmithKline

All conflicts were resolved through peer review.

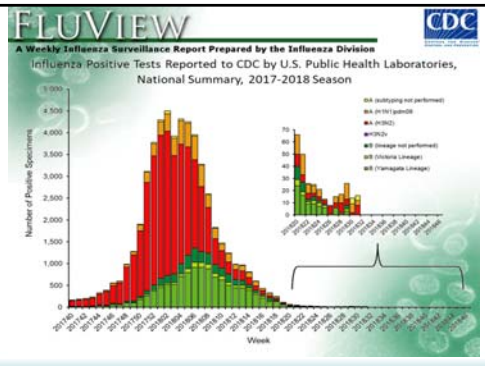
Program Objectives

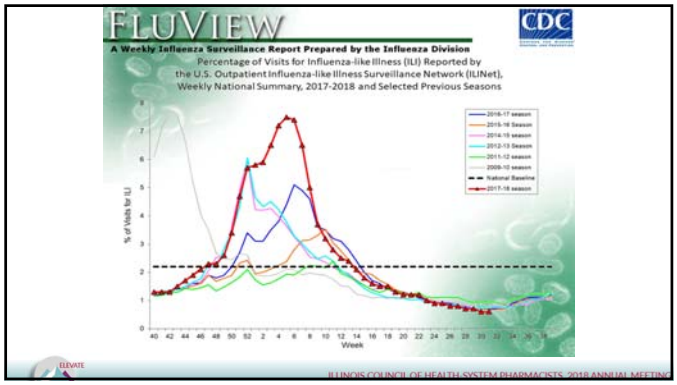
- Pharmacists
  - Assess data about the impact of influenza illness and vaccine effectiveness
  - Evaluate evidence regarding strategies to optimize vaccination rates for patients and health care workers
  - Propose factors to consider in product selection of influenza vaccines
  - Apply knowledge regarding influenza vaccine and antiviral therapies to clinical scenarios
- Pharmacy Technicians
  - Evaluate information regarding the impact of influenza and influenza vaccine on patient outcomes
  - Design strategies to improve knowledge and awareness regarding influenza and the vaccine
  - Propose pharmacy-based activities to optimize influenza vaccination rates

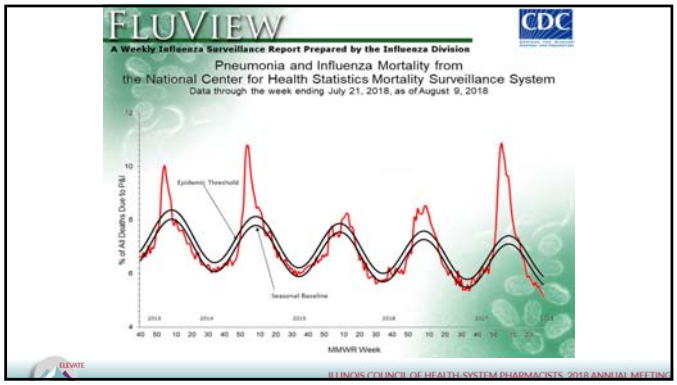
2017-18 Influenza Season: A Review

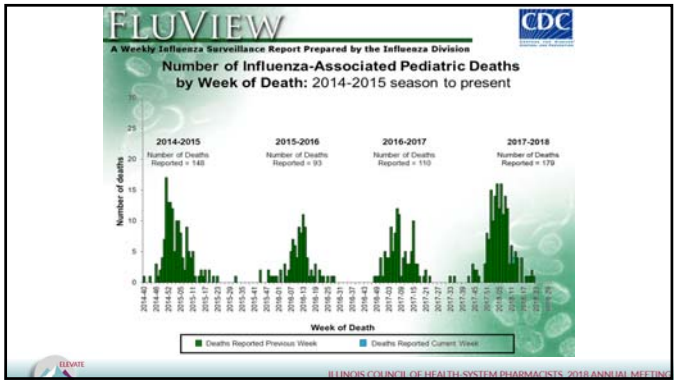
- A particularly harsh season
- Activity detected in November and extending into March
- An influenza A strain (H3N2) was predominant, although influenza B was responsible for most cases late in the season
- Over 99% of all strains assessed were susceptible to neuraminidase inhibitor antiviral agents

MMWR 2018; 67(22): 634-642



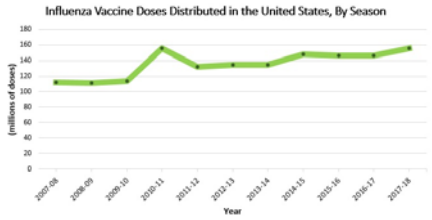

FLUVIEW
A Weekly Influenza Surveillance Report Prepared by the Influenza Division
CDC
Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, 2017-2018 and Selected Previous Seasons
% of Visits for ILI
Week
2016-17 season
2015-16 Season
2014-15 season
2012-13 Season
2011-12 season
2009-10 season
National Baseline
2017-18 season
ELEVATE
ILLINOIS COUNCIL OF HEALTH-SYSTEM PHARMACISTS: 2018 ANNUAL MEETING


FLUVIEW
A Weekly Influenza Surveillance Report Prepared by the Influenza Division
CDC
Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System
Data through the week ending July 21, 2018, as of August 9, 2018
% of All Deaths Due to P&I
Epidemic Threshold
Seasonal Baseline
MMWR Week
ELEVATE
ILLINOIS COUNCIL OF HEALTH-SYSTEM PHARMACISTS: 2018 ANNUAL MEETING

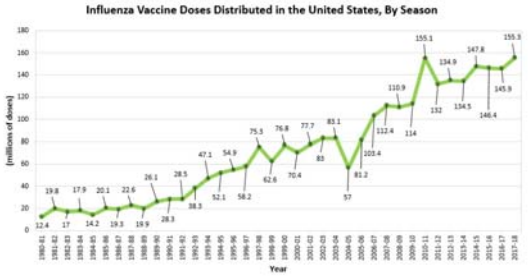

FLUVIEW
A Weekly Influenza Surveillance Report Prepared by the Influenza Division
CDC
Number of Influenza-Associated Pediatric Deaths by Week of Death: 2014-2015 season to present
2014-2015
Number of Deaths Reported = 148
2015-2016
Number of Deaths Reported = 93
2016-2017
Number of Deaths Reported = 110
2017-2018
Number of Deaths Reported = 179
Number of deaths
Week of Death
Deaths Reported Previous Week
Deaths Reported Current Week
ELEVATE
ILLINOIS COUNCIL OF HEALTH-SYSTEM PHARMACISTS: 2018 ANNUAL MEETING

Influenza Vaccine: Supply and Vaccination Rates

Influenza Vaccine Supply



https://www.cdc.gov/flu/about/qa/vaxsupply.htm

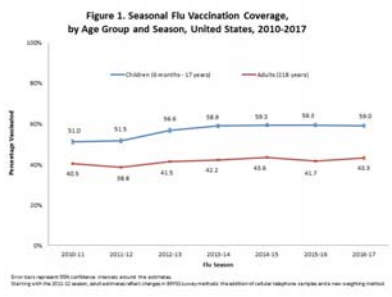


https://www.cdc.gov/flu/about/qa/vaxsupply.htm

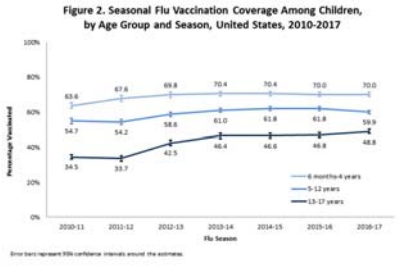
2017-18 Influenza Vaccine Supply

Estimated Supply 151-166 million
Thimerosal-free: 130 million
Quadrivalent: 119 million

https://www.cdc.gov/flu/about/qa/vaxsupply.htm



https://www.cdc.gov/flu/fluvaxview/coverage-1617estimates.htm



https://www.cdc.gov/flu/fluvaxview/coverage-1617estimates.htm

Influenza Vaccine Coverage Rates for Persons 18 years of Age and Older, 2016-17

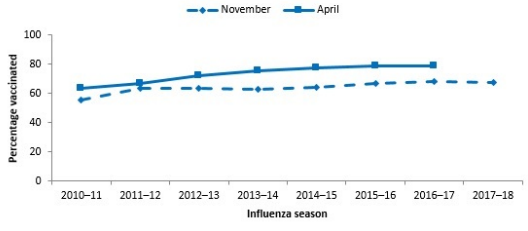
Age Group	Unweighted Sample Size	%[‡] ± 95% CI[§]	Difference from the 2015–16 Season ± 95% CI
≥18 years	325,801	**43.3** ± 0.6	1.6 ± 0.7[‖]
18–64 years	206,532	**37.5** ± 0.6	1.2 ± 0.8[‖]
18–64 years with high risk conditions[¶]	54,748	**46.4** ± 1.2	0.4 ± 1.7
18–64 years without high risk conditions	149,533	**34.9** ± 0.8	1.4 ± 1.0[‖]
18–49 years	107,527	**33.6** ± 0.8	0.9 ± 1.1
18–49 years with high risk conditions	19,092	**39.3** ± 1.8	-0.2 ± 2.7
18–49 years without high risk conditions	87,094	**32.6** ± 0.8	1.1 ± 1.1
50–64 years	99,005	**45.4** ± 1.0	1.8 ± 1.3[‖]
≥65 years	119,269	**65.3** ± 1.0	1.9 ± 1.3[‖]

https://www.cdc.gov/flu/fluvaxview/coverage-1617estimates.htm

What is the Healthy People 2020 Goal for influenza vaccination rates among health care personnel?

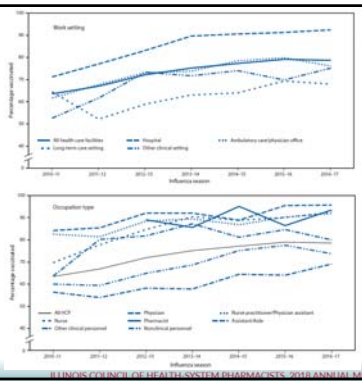
A. 50%
B. 70%
C. 80%
D. 90%

Flu vaccination coverage among health care personnel vaccinated by November and by April for 2010–11 through 2016–17 flu seasons, and by November for 2017–18 flu season, Internet panel survey, United States



https://www.cdc.gov/flu/fluvaxview/hcp-ips-nov2017.htm

Influenza Vaccine Rates among Health Care Personnel

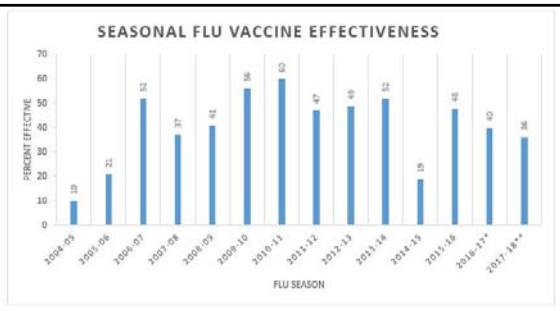


MMWR 2017; 66(38);1009–1015. Available at: https://www.cdc.gov/mmwr/volumes/66/wr/mm6638a1.htm#F1_down

2017-18 Influenza Vaccination Rates for Health Care Personnel (Early Season Estimates)

- Overall, early-season rate for health care personnel was 67.6%
- Occupation:
  - Pharmacists 86.4%
  - Physicians 82.7%
  - Nurses 80.9%
  - NP/PA 79.7%
- Employment location:
  - Hospitals 82.6%
  - Ambulatory Clinics 68.7%
  - Long-term Care 58.5%
- Most common reasons for not receiving vaccine:
  - Fear of side effects or getting sick from vaccine 22.1%

https://www.cdc.gov/flu/fluvaxview/hcp-ips-nov2017.htm



Available at: https://www.cdc.gov/flu/images/professionals/vaccination/seasonal-flu-vaccine-effeciveness.jpg

2018-19 Influenza Vaccine Composition

- Trivalent Vaccine
  - A/Michigan/45/2015 A(H1N1)pdm09-like virus
  - A/Singapore/INFIMH-16-0019/2016 A(H3N2)-like virus*
  - B/Colorado/06/2017-like (B/Victoria lineage) virus*
- Quadrivalent
  - Above antigens, plus
  - B/Phuker/3073/2013-like (B/Yamagata lineage) virus

* Indicates new component for 2018-19 compared to 2017-18 Northern Hemisphere version

MMWR 2018; 67(22): 634-642

2018-19 Influenza Vaccine Recommendation Highlights

- Vaccination with an influenza vaccine remains the most effective strategy to prevent influenza illness
- Routine annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications
- Vaccination should be offered by the end of October if possible
- Some children aged 6 months through 8 years will require 2 doses
- Intranasal, live, attenuated influenza vaccine (LAIV4), which has not been recommended since the 2015-16 season, is an option for the 2018-19 influenza season
- No preference is expressed for any specific influenza vaccine product

Influenza Vaccine Effectiveness

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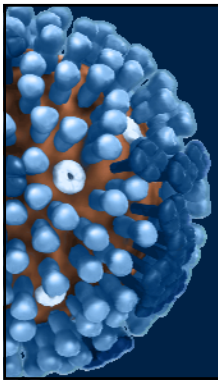
Which of the following are independent effects of vaccination against influenza?

A. "Herd" or community immunity against influenza
B. Reduction in influenza-like illnesses ("The Flu")
C. Lower risk of myocardial infarction in patients with CHD
D. Reduced ICU admissions among people 65 years of age or older
E. Each of the above

Acknowledgements

Vaccine Effectiveness Slides used in today's presentation were provided courtesy of:

- Daniel Jernigan, MD, MPH, Director, Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC)



Vaccine Effectiveness

Monitoring Influenza Vaccine Effectiveness Using Test-Negative Control Design (TND)

US Flu VE Network*

Season	VE against A/B influenza viruses (95% CI)
2010-11	60% (53, 66)
2011-12	47% (36,56)
2012-13	49% (43, 55)
2013-14	52% (44,59)
2014-15	19% (10,27)
2015-16	48% (41, 55)
2016-17	40% (32, 46)

Preliminary adjusted vaccine effectiveness against medically attended influenza by age group 2017–18 for any Influenza A or B virus infection

	Influenza positive		Influenza negative		Vaccine Effectiveness: Unadjusted		Vaccine Effectiveness: Adjusted*	
Any influenza A or B virus	N vaccinated /Total	(%)	N vaccinated /Total	(%)	VE %	95% CI	VE %	95% CI
Overall	1296/3097	(42)	2969/5538	(54)	38%	(32 to 43)	**40%**	**(34 to 46)**
Age group (yrs)								
6 mos–8	201/616	(33)	760/1380	(55)	60%	(52 to 68)	**53%**	**(42 to 62)****
9–17	166/529	(31)	221/584	(38)	25%	(4 to 41)	**29%**	**(8 to 46)**
18–49	315/966	(33)	813/1893	(43)	36%	(24 to 45)	**35%**	**(23 to 46)**
50–64	301/571	(53)	583/938	(62)	32%	(16 to 45)	**33%**	**(17 to 47)**
≥65	313/415	(75)	592/743	(80)	22%	(-4 to 41)	**20%**	**(-9 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. ** P-value <0.001 for age group-VE interaction term compared to all other ages combined.

Preliminary adjusted vaccine effectiveness against medically attended influenza A(H3N2) by age group, 2017–18

	Influenza positive		Influenza negative		Vaccine Effectiveness: Unadjusted		Vaccine Effectiveness: Adjusted*	
	N vaccinated /Total	(%)	N vaccinated /Total	(%)	VE %	95% CI	VE %	95% CI
Influenza A/H3N2								
Overall	813/1790	(45)	2969/5538	(54)	28%	(20 to 35)	**24%**	**(15 to 33)**
Age group (yrs)								
6 mos–8	131/337	(39)	760/1380	(55)	48%	(34 to 59)	**37%**	**(17 to 52)****
9–17	118/335	(35)	221/584	(38)	11%	(-18 to 32)	**10%**	**(-23 to 35)**
18–49	218/581	(38)	813/1893	(43)	20%	(3 to 34)	**14%**	**(-6 to 30)**
50–64	166/298	(56)	583/938	(62)	23%	(0 to 41)	**25%**	**(0 to 44)**
≥65	180/239	(75)	592/743	(80)	22%	(-10 to 45)	**17%**	**(-22 to 44)**

* Multivariable logistic regression models adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrollment, and calendar time. ** P-value = 0.05 for age group-VE interaction term compared to all other ages combined.

Preliminary adjusted vaccine effectiveness against medically attended influenza A(H1N1)pdm09 by age group, 2017–18

	Influenza positive		Influenza negative		Vaccine Effectiveness			
					Unadjusted		Adjusted*	
	N vaccinated /Total	(%)	N vaccinated /Total	(%)	VE %	95% CI	VE %	95% CI
Influenza A/H1N1pdm09								
Overall	96/326	(29)	2969/5538	(54)	64%	(54 to 72)	**65%**	**(55 to 73)**
Age group (yrs)								
6 mos–17	26/154	(17)	981/1964	(50)	80%	(69 to 87)	**82%**	**(71 to 88)**
18–49	27/99	(27)	813/1893	(43)	50%	(22 to 68)	**48%**	**(17 to 67)**
50–64	18/40	(45)	583/938	(62)	50%	(6 to 74)	**45%**	**(-6 to 72)**
≥65	25/33	(76)	592/743	(80)	20%	(-80 to 65)	**10%**	**(-116 to 63)**

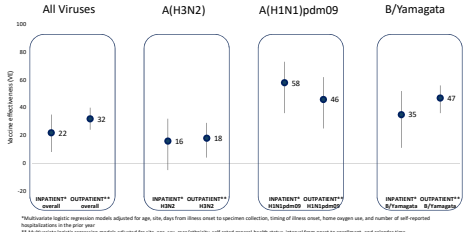
* Multivariable logistic regression models adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrollment, and calendar time.

Preliminary adjusted vaccine effectiveness against medically attended influenza B by age group, 2017–18

	Influenza positive		Influenza negative		Vaccine Effectiveness			
					Unadjusted		Adjusted*	
	N vaccinated /Total	(%)	N vaccinated /Total	(%)	VE %	95% CI	VE %	95% CI
Influenza B/Yamagata								
Overall	372/917	(41)	2969/5538	(54)	41%	(32 to 49)	**49%**	**(40 to 56)**
Age group (yrs)								
6 mos–8	44/130	(34)	760/1380	(55)	58%	(39 to 71)	**46%**	**(19 to 64)**
9–17	45/161	(28)	221/584	(38)	36%	(7 to 57)	**39%**	**(9 to 59)**
18–49	68/268	(25)	813/1893	(43)	55%	(40 to 66)	**57%**	**(42 to 68)**
50–64	108/216	(50)	583/938	(62)	39%	(18 to 55)	**45%**	**(24 to 60)**
≥65	107/142	(75)	592/743	(80)	22%	(-19 to 49)	**29%**	**(-12 to 55)**
Influenza B/Victoria								
Overall	8/39	(21)	2969/5538	(54)	78%	(51 to 90)		

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

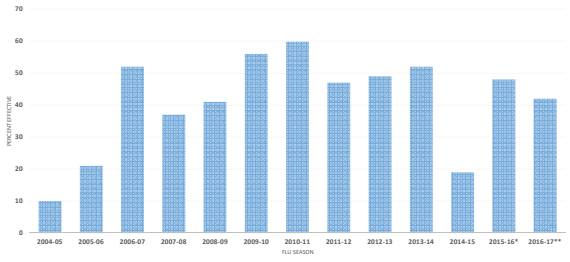
Preliminary VE estimates by virus type among inpatient and outpatient adults aged ≥18 years, 2017-18



*Multivariate logistic regression models adjusted for age, site, days from illness onset to specimen collection, timing of illness onset, home oxygen use, and number of self-reported hospitalizations in the prior year
** Multivariate logistic regression models adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrollment, and calendar time

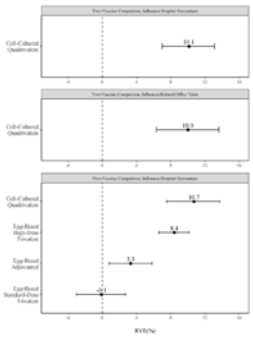
Seasonal Influenza Vaccine Effectiveness

Centers for Disease Control and Prevention 2005 – 2017



Relative Vaccine Effectiveness (RVE) of Different Vaccines for ≥65 yo's*

- Population: Medicare Fee-for-service beneficiaries who received the cell-cultured or any of four egg-based influenza vaccinations for the 2017-18 season
- Cell-cultured vaccines were 10.7% (95% CI 7.5, 13.7) more effective
- High-dose egg-based vaccines were 8.4% (95% CI 6.6, 10.1) more effective
- Adjuvanted egg-based vaccines were 3.3% (95% CI 1.2, 6.0) more effective



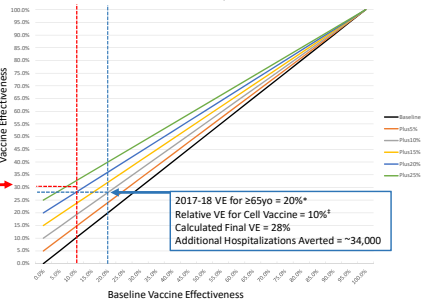
Combined Baseline and Relative Vaccine Effectiveness (VE) Estimates for Relative VE Improvements of 5% to 25%

2012-13 VE for ≥65yo = 11%*

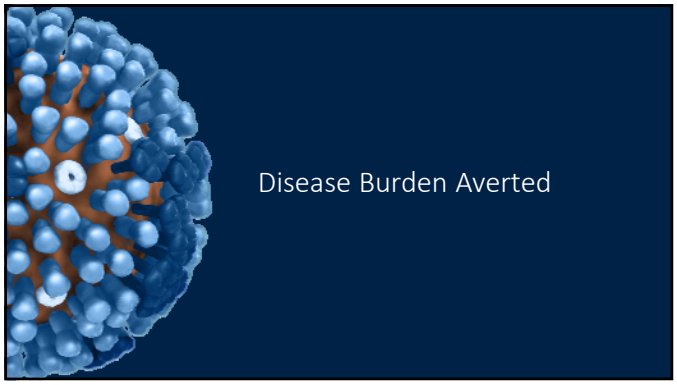
Relative VE for Hi-Dose = 22%†

Calculated Final VE = 31%

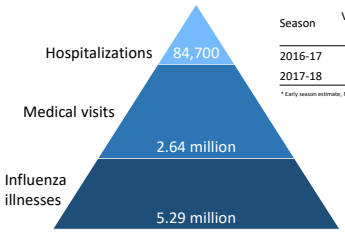
Additional Hospitalizations Averted = ~44,000



2017-18 VE for ≥65yo = 20%*
Relative VE for Cell Vaccine = 10%‡
Calculated Final VE = 28%
Additional Hospitalizations Averted = ~34,000



Current influenza vaccines reduce the burden of illnesses in the US

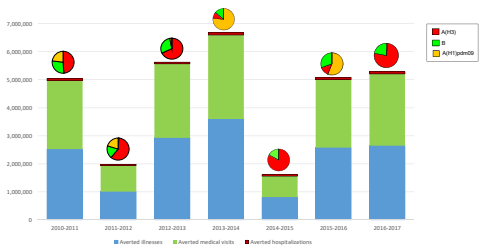


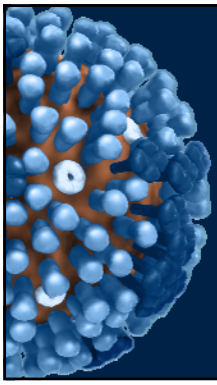
Season	Vaccine coverage % (95% CI)	Vaccine effectiveness % (95% CI)
2016-17	40 (38–43) *	40 (32–46)
2017-18	39 (37–40) *	40 (34–46)

* Early season estimate, Nov 2016 and Nov 2017

Estimates of 2017-18 averted burden expected in fall 2018

Influenza Burden Averted 2010-2017





Attenuation of Disease

Data on Disease Attenuation

- Overall, data on attenuation comes from observational studies, most of which are only one season and often under-powered to adequately address attenuation of the spectrum of influenza disease
- Studies span the spectrum of association with prevention of severe disease to association with severe disease
  - Studies vary in age groups, seasons, study design
- Reported improved outcomes associated with vaccine include:
  - Death
  - ICU admission and duration
  - Hospital admission and duration
  - Fever
  - Combined symptom scores
  - Lower respiratory tract illness

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA hivma

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

- Study conducted through CDC hospitalization surveillance (FluSurvNet) in 2013-14 H1N1 season with overall VE for all ages = 52%
- Data for 4,910 hospitalized aged ≥18 yo
  - ~1/3 each for ≥18, 50-64, ≥65 yo
- Excluded institutionalized persons and those not treated with antiviral drugs since >80% had received oseltamivir
- Used Propensity Score Matching to address bias
- Prior similar study in 2012-13 H3N2 season found no significant findings

Vaccine Had Statistically Significant Impact in 2013-14

Ariola et al CID 2018

- Reduction in in-hospital death
  - 79% in 18-49 yo
  - 52% in 50-64 yo
  - 61% in ≥65 yo
- Reduction in ICU admissions
  - 37% in 18-49 yo
  - 37% in ≥65 yo
- Earlier discharge from ICU
  - 32% in 50-64 yo
  - 36% in ≥65 yo
- Earlier discharge from hospital
  - 13% in 50-64 yo
  - 24% in ≥65 yo

Selected Studies on Disease Attenuation

- VE against hospitalization in ≥65yo = 43% (22-59%), higher against ICU admission (70%) and death (76%) (Andrew 2017)
- VE against severe disease in ≥65yo = 43% (2-67%) (Casado 2016)
- VE against severe disease in all ages = 58% (20-88%) (Castilla 2013)
- VE no different in- vs outpatient over six seasons in all ages (Castilla 2018)
- Milder disease among vaccinated individuals infected with H3N2 viruses during the 2009–2014 seasons (Deiss 2015)
- VE no different in- vs out-patient over six seasons (Feng 2016)
- Reduction of 80% of lower respiratory tract illness and 70% of temperature above 39C in RCT of 3-8yo (Jain 2013)
- Vaccine associated with worse outcomes in 70 VA patients (Joshi 2015)
- No association between influenza vaccination and a reduction in the risk of hospital admission for ≥20 yos at Marshfield Clinic (McLean 2013)
- Vaccine reduced hospitalization and pneumonia in nursing home patients (Patriarca 1985)
- VE higher among inpatients (Petrie 2016)
- Vaccine associated with shorter duration of fever in elderly (Ruben 1974)
- No association between influenza vaccination and a reduction in the risk of hospital admission in influenza-confirmed patients (Van Wormer 2014)

The Tale of Two "Influenzas"? (Not really)

Walter is a 75 year old man, active and independent in his community
- Closely follows a healthy diet and exercises daily
- Because he is healthy, he refuses flu vaccine because he doesn't see the need
- Dies from influenza illness contracted on a cruise ship.

Joe is also a 75 year old man, active and independent in his community
- Follows a healthy diet, has a history of CVD & diabetes, does not exercise daily
- Receives annual flu vaccination
- Develops medically attended influenza while on a cruise ship; survives

Courtesy, Dr. McElhaney, 2018.

Case Scenario: Influenza Outcomes

Ann is 53 years old with Type 2 Diabetes and chronic lung disease (previously a smoker)

- Admitted to hospital with influenza, transferred to ICU and required intubation.
- Prior to influenza illness, diabetes and lung disease were well controlled and stable on medications.
- During ICU stay, experienced acute confusion for 2 days.
- Upon discharge home, experienced permanent loss of independence in activities of daily living due to physical limitations as a result of influenza.
- She had not been vaccinated in the current season, nor had anyone in her household.

Courtesy, Dr. McElhaney. 2018.

At Your Tables, Discuss:

- What were Anne's risk factors for poor outcomes from influenza infection?
- Why is influenza such a "bad" infection in patients like Anne?
- What data, if any, tells us whether or not flu vaccine would have prevented Anne's situation?
- Is Anne's situation of long term loss of independence following influenza infection unusual?
- What antivirals would have been optimal during her hospitalization?
- What preventive steps should have been taken to reduce risk of household contacts from developing influenza illness?

Select groups for report

How long does the increased risk for mortality persist for a patient with cardiovascular disease who develops acute influenza?

A. During hospitalization only
B. 7 days post discharge
C. 30 days post discharge

The impact of influenza goes well beyond the infection rates…

- Influenza has been shown to seriously exacerbate chronic health conditions, including asthma, COPD, and chronic heart disease.
- Infection triggers an inflammatory response, especially in the respiratory tract, which can lead to sepsis.
- Serious illness and death is most likely to occur in patients with underlying chronic disease and in patients over 65 years of age regardless of underlying condition.
- Myocarditis, encephalitis, myositis, and rabdomyolysis are all serious, potential complications of the inflammatory response caused by influenza.

Influenza Vaccines

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Let's Review – Patients at Higher Risk of Medical Complications Due to Influenza

- all children aged 6 through 59 months;
- all persons aged ≥50 years;
- adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus);
- persons who are immunocompromised due to any cause (including immunosuppression caused by medications or by HIV infection);
- women who are or will be pregnant during the influenza season;
- children and adolescents (aged 6 months through 18 years) who are receiving aspirin- or salicylate-containing medications and who might be at risk for experiencing Reye syndrome after influenza virus infection;
- residents of nursing homes and other long-term care facilities;
- American Indians/Alaska Natives; and
- persons who are extremely obese (BMI ≥40).

MMWR. 2017;66(2):1-20.

Let's Review – Patients at Higher Risk of Medical Complications Due to Influenza

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- persons who are extremely obese (BMI ≥40).

MMWR. 2017;66(2):1-20.

To put it in perspective…As of July 31, 2018

- 328,210,000 people in the United States
  - 20,020,810 are younger than 5 years of age.
  - 51,200,760 are older than 65 years of age.
    - 10,000 people will celebrate their 65th birthday every day through 2030
- There are a lot of healthcare providers:
  - 861,000 practicing physicians
  - 3,853,000 active registered nurses
  - 312,500 licensed pharmacists

AAMC Workforce Report 2016.
United States Census Bureau Website, 2018.
National Nursing Workforce Survey 2015.
U.S. Bureau of Labor and Statistics Website, 2016.

Influenza Vaccine Formulations* United States, 2018-19

- **IIV4, Standard Dose**
  - Fluarix (≥3 y.o.)
  - Flulaval (≥3 y.o.)
  - Fluzone (≥6 months)
- **ccIIV4, Standard Dose**
  - Flucelvax (≥4 y.o.)
- **RIV4**
  - Flublok (≥18 y.o.)
- **LAIV4**
  - FluMist (2 to 49 y.o.)
- **IIV3, Standard Dose**
  - Afluria (≥9 y.o.)
  - Fluvirin (≥4 y.o.)
- **aIIV3, Standard Dose**
  - Fluad (≥65 y.o.)
- **IIV3, High Dose**
  - Fluzone High-Dose (≥65 y.o.)

IIV4, quadrivalent inactivated influenza vaccine. ccIIV4, cell-cultured, quadrivalent inactivated influenza vaccine. RIV4, recombinant quadrivalent inactivated influenza vaccine. LAIV4, live, attenuated, quadrivalent influenza vaccine. IIV3, trivalent inactivated influenza vaccine. aIIV3, adjuvanted trivalent inactivated influenza vaccine.

*Anticipated based upon FDA approvals and manufacturer websites

Case Scenario: Influenza Vaccine Inventory

You are in charge of inventory management for both inpatient and outpatient services in your health system. The infection control committee has decided to intensify its efforts to prevent influenza infection through vaccination of staff and patients. They've asked the pharmacy department to ensure adequate supply for a) inpatient utilization, b) staff immunization, and c) outpatient clinic and pharmacy utilization.

At your Tables, Discuss:

- How will you decide the quantity of vaccine to order?
- Which vaccine products for influenza should you order?
- When should you order flu vaccine for best pricing and priority shipping?
- If you were to receive limited quantities of influenza vaccine, how would you prioritize which patients/clinics receive vaccine supply first?
- A patient receiving influenza vaccine experiences the very rare occurrence of anaphylaxis. What federally mandated reporting of this event must occur?

Select groups for report

At your institution, you received a limited supply of IIV4 in August and it is depleted in mid-September. You have IIV3 and are promised a new shipment of IIV4 in a month. What is an appropriate policy for patients now?

A. Administer IIV3 to high risk patients now, and revaccinate them when the IIV4 supply arrives.
B. Defer high risk patients until the new supply of IIV4 arrives
C. Vaccinate all patients with the currently available vaccine until the new supply arrives.

Quadrivalent Live Attenuated Influenza Vaccine (LAIV4)

- Intranasal administration
- Licensed by FDA and recommended by ACIP from 2013-14 through 2015-16 years as appropriate for otherwise health children and adults ages 2 – 49 years.
- Retrospective data analysis showed low effectiveness against A(H1N1)pdm09-like viruses.
- ACIP withdrew their support of the vaccine, and recommended that it NOT be used for the 2016-17 and 2017-18 seasons.
- Manufacturer maintained licensure of the product, began conducting studies on alternate vaccine strains

MMWR. June 8, 2018: 67(22); 643-45.

LAIV4 – Replacement Strains of A(H1N1)

- Manufacturer conducted a shedding and immunogenicity study in 2017-18 (Not an effectiveness study)
- Replicative fitness of vaccine virus strains is a known issue in influenza vaccine production, particularly with egg-based products.
- A/Bolivia/H1N1 was the reduced effectiveness strain; tested using an A/Slovenia/H1N1
- A/Slovenia immune responses were similar to those seen with highly effective pre-pandemic LAIV H1N1 strain.
- A new strain selection process will be applied to all future LAIV strains

CDC. Results of randomized trial of a new H1N1 LAIV strain in US children. Presented to the Advisory Committee on Immunization Practices, February 21, 2018. Atlanta, GA: US Department of Health and Human Services, CDC; 2018.

LAIV4 – 2018-19 Season

- ACIP again recommends use of the LAIV4 as an option for age-appropriate vaccination.
  - Committee recognized that removal in LAIV4 as an option led to an approximately 2% decline in pediatric influenza immunization rates.
  - Immunogenicity and shedding data compelled the ACIP to offer as a means to improve coverage, especially in school-based settings.
- American Academy of Pediatrics has a differing recommendation:
  - Recommends parents have children immunized preferentially with the injectable vaccine; reserving LAIV4 as a last resort only if a child would not otherwise be vaccinated
    - "Recent history has shown the injected form of the vaccine to be more consistent in protecting against more strains of the flu virus."

MMWR. June 8, 2018: 67(22); 643-45.
American Academy of Pediatrics Press Release. May 21, 2018.

Which of the following individuals would NOT be a candidate for Live, attenuated influenza vaccine?

A. 5-year-old health child
B. 30-year-old healthy community pharmacist
C. 25-year-old nurse working with patients on isolation precautions due to bone marrow transplant
D. 12-year-old adolescent with ADHD diagnosis
E. Any of these people

IIV3, High Dose

- Data from 1986-2002 shows that antibody response to standard dose influenza vaccine is substantially lower in persons ≥ 65 years of age compared to young adults (17-53% vs. 70-90%).
- HD Contains four times the HA antigen contained in standard dose.
  - (60µg vs 15µg HA)
- Licensed for use in 2009 based upon immunogenicity data.
- Manufacturer was required to provide FDA with efficacy data post-licensure.

Goodwin K, Viboud C, Simonsen L. Vaccine. 2006; 24(8):1159-69.

IIV3
High Dose (HD) versus Standard Dose (SD)

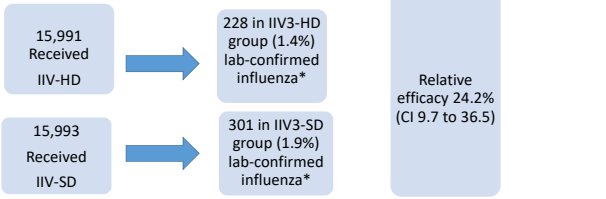
Regarding Immunogenicity:

Geometric mean titers were significantly higher in the HD vaccine	
A/H1N1	GMT 481.8 (457.7-507.1) for HD versus 271.8 (257.4-287.1) for SD
A/H3N2	GMT 685.5 (651.4-721.4) for HD versus 349.8 (332.1-368.6) for SD
B	GMT 138.1 (132.2-144.2) for HD versus 97.6 (93.3-102.0) for SD

N Engl J Med. 2014 Aug 14;371(7):635-45.

IIV3
High Dose (HD) versus Standard Dose (SD)

31,989 Participants (126 North American Research Centers)



*Includes Intention to Treat Analysis

N Engl J Med. 2014 Aug 14;371(7):635-45.

What needs to be studied?

- Would HD influenza vaccine provide better vaccine effectiveness in immunocompromised patients?
  - At least one study suggests it might.
- If HD vaccine produces higher titers in older adults where the immune system is less responsive, wouldn't HD vaccine be better in younger adults or children?
  - Studies so far in younger populations have been inconclusive, but under-powered.

Biol Blood Marrow Transplant. 2016 Mar;22(3):528-35.

Adverse Event Profile, IIV3 High Dose

Table 1: Study 1*: Frequency of Solicited Injection-Site Reactions and Systemic Adverse Events Within 7 Days After Vaccination with Fluzone High-Dose or Fluzone, Adults 65 Years of Age and Older

	Fluzone High-Dose (N[b]=2569-2572) Percentage			Fluzone (N[b]=1258-1260) Percentage		
	Any	Moderate[c]	Severe[d]	Any	Moderate[c]	Severe[d]
Injection-Site Pain	35.6	3.7	0.3	24.3	1.7	0.2
Injection-Site Erythema	14.9	1.9	1.8	10.8	0.8	0.6
Injection-Site Swelling	8.9	1.6	1.5	5.8	1.3	0.6
Myalgia	21.4	4.2	1.6	18.3	3.2	0.2
Malaise	18.0	4.7	1.6	14.0	3.7	0.6
Headache	16.8	3.1	1.1	14.4	2.5	0.3
Fever[e] (≥99.5°F)	3.6	1.1	0.0	2.3	0.2	0.1

a NCT00391053 b N is the number of vaccinated participants with available data for the events listed c Moderate - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site erythema and Injection-site swelling: ≥2.5 cm to 100.4°F to ≤102.2°F; Myalgia, Malaise, and Headache: interferes with daily activities d Severe - Injection-site pain: incapacitating, unable to perform usual activities; Injection site erythema and Injection-site swelling: ≥5 cm; Fever: >102.2°F; Myalgia, Malaise, and Headache: prevents daily activities e Fever - The percentage of temperature measurements that were taken by oral route or not recorded were 97.9% and 2.1%, respectively, for Fluzone High-Dose; and 98.6% and 1.4%, respectively, for Fluzone

Fluzone High-Dose Packing Insert. Sanofi Pasteur. Swiftwater, PA

Adjuvanted Vaccine (aIIV3)

- Contains a standard antigen load 15µg HA
- Contains MF-59® Adjuvant (Novartis)
  - Squalene-based oil-in-water emulsion
  - Practical: Product needs to be shaken before administration (suspension)
- Currently FDA-approved for use in individuals ≥ 65 years of age.
- Study complete and submitted to FDA for possible approval for use in children

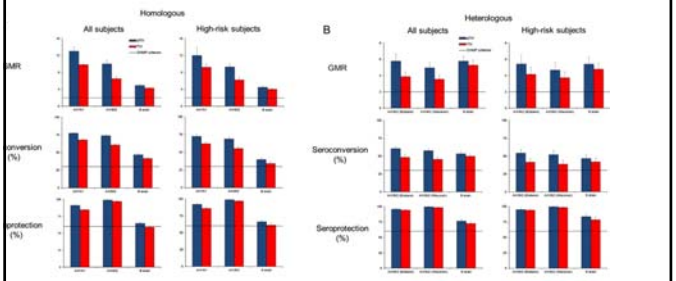
Vaccine. 2013 Dec 9;31(51):6122-8.

Immunogenicity of MF-59 Adjuvanted Flu Vaccine

- Randomized, observer-blinded trial comparing aIIV3 to IIV3.
  - U.S., Panama, Columbia, the Philippines
- Statistically powered to assess immunogencity and seroconversion
  - Study was not powered adequately to show clinical effectiveness although authors did report effectiveness data.
- Equally matched groups of 3500 participants
  - Titers drawn at 22 days, 180 days, and 365 days post vaccination.
  - GMT of >2.0 above baseline considered adequate immunogenicity

Frey et al. Vaccine. 2104; 32(39):5027-34

Immunogenicity



Frey et al. Vaccine. 2104; 32(39):5027-34

Efficacy of MF-59 Adjuvanted Flu Vaccine in Patients ≥ 65 Years of Age

- 11 studies enrolled 546,056 patients
  - 6 case control; 2 cohort; 2 prospective, community-based case control
  - Italy, Spain, Canada
  - 52.3% of all patients received aIIV3 (MF59)
- Authors conclude that available data over 20 years demonstrates VE at least as good as traditional IIV3;
  - May be some benefit over traditional IIV3 for A strain influenzas in particular

Recombinant HA Flu Vaccine (rIIV3)

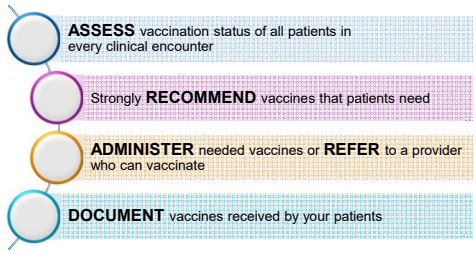
- Contains recombinant HA proteins to the three influenza viruses using insect cell lines for production of the vaccine
  - No eggs/egg protein
- Exact genetic match to reference strain; less potential for ”drift”
- Expedited

Best Practices for Flu Vaccine

Key Resources for Every Clinician

- CDC Storage and Handling Toolkit
  - https://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/index.html
  - Note: ALL persons with responsibility for vaccine supply should be required to view the 1-hour on-line module (1 C.E.U. is provided)
- CDC’s Vaccine Administration Resources
  - https://www.cdc.gov/vaccines/hcp/admin/admin-protocols.html
  - Note: Especially important for all NEW employees administering vaccine
- Vaccine Adverse Event Reporting System
  - https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html
  - Note: Recommend bookmarking this page on all in-house computers

Standards for Adult Vaccination



Centers for Disease Control and Prevention. Standards for adult immunization practice: Overview. cdc.gov/vaccines/hcp/patient-ed/adults/for-practice/standards/index.html. Accessed 2/7/2017.

Screening Patients Prior to Vaccination

- Represents an important component of the process of providing vaccine services
- Purpose is to identify patient's status to receive vaccine, identify possible precautions or contraindications, and determine other possible vaccines to administer

Sample Screening Questions for Influenza Vaccine

- "How are you feeling today?"
  - The patient can receive vaccine unless you plan to refer them to another health professional now
- "What allergies do you have?"
  - Only relevant one for influenza would be serious egg allergy in which you might refer or be prepared to manage an allergic response
- "Have you ever experienced a serious adverse reaction to the influenza vaccine previously?"
  - Universal contraindication to any vaccine is a serious adverse reaction previously
- "What other medical conditions do you have?"
  - Helps to identify other vaccines to consider
- For live intranasal influenza vaccine
  - Are you pregnant?
  - Do you have any immunocompromising conditions or take immunosuppressive therapy?

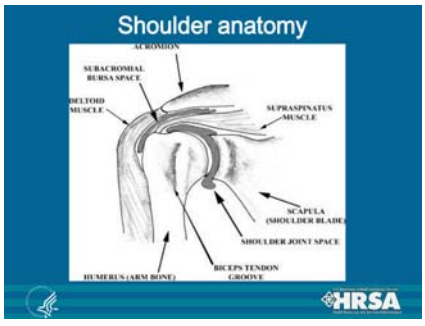
The acronym, SIRVA, refers to:

A. The reporting process for a patient experiencing an adverse reaction to a vaccine.
B. The reporting process for a patient receiving the wrong vaccine.
C. The procedures to follow for an allergic reaction.
D. A possible shoulder injury related to improper vaccine administration.

Shoulder Injury Related to Vaccine Administration (SIRVA)

- SIRVA is thought to result from the unintentional injection of a vaccine into tissues and structures lying underneath the deltoid muscle of the shoulder
- The Institute of Medicine (IOM) reviewed the scientific and medical literature finding that the evidence convincingly supported a causal relationship between vaccine administration and deltoid bursitis
- Atanasoff et al. published a case series reporting the experience of the Vaccine Injury Compensation Program with regard to shoulder injuries following vaccination. The IOM reviewed this article and commented that the cases were consistent with deltoid bursitis.

www.hrsa.gov/advisorycommittees/childhoodvaccines/Meetings/20150604/sirva.pdf



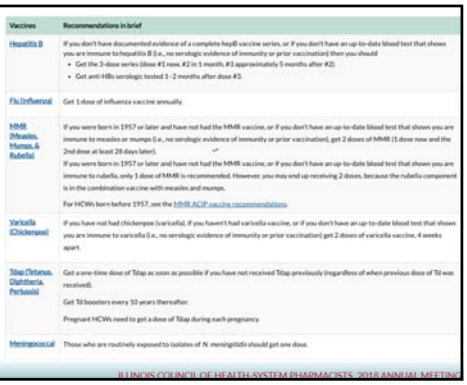
Preventing SIRVA

- Follow CDC guidance for appropriate needle length selection[1]
- Ensure proper administration technique for intramuscular injections
  - Central portion of deltoid
  - Avoid the top 1/3 of the deltoid[2]
- Comprehensive, skills-based training should be integrated into existing staff education programs such as new staff orientation and annual education requirements[1]
- Persons administering vaccine should be in the same seated position as the patient. Avoid standing to administer vaccine to a patient who is seated. [2]

1. ACIP General Practice Recommendations. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/administration.html
2. ACIP October 2017 Presentation of Dr. Andrew Kroger, CDC

Pharmacists and Pharmacy Technicians Need to be Vaccinated Too!

Immunization of HCW: Recommendations of ACIP. *MMWR*. 2011; 60(RR07):1-45.



Vaccines	Recommendations in brief
Hepatitis B	If you don't have documented evidence of a complete hepB vaccine series, or if you don't have an up-to-date blood test that shows you are immune to hepatitis B (i.e., no serologic evidence of immunity or prior vaccination) then you should • Get the 3-dose series (dose #1 now, #2 in 1 month, #3 approximately 5 months after #2). • Get anti-HBs serologic tested 1-2 months after dose #3.
Flu (Influenza)	Get 1 dose of influenza vaccine annually.
MMR (Measles, Mumps, & Rubella)	If you were born in 1957 or later and have not had the MMR vaccine, or if you don't have an up-to-date blood test that shows you are immune to measles or mumps (i.e., no serologic evidence of immunity or prior vaccination), get 2 doses of MMR (1 dose now and the 2nd dose at least 28 days later). If you were born in 1957 or later and have not had the MMR vaccine, or if you don't have an up-to-date blood test that shows you are immune to rubella, only 1 dose of MMR is recommended. However, you may end up receiving 2 doses, because the rubella component is in the combination vaccine with measles and mumps. For HCWs born before 1957, see the MMR ACIP vaccine recommendations.
Varicella (Chickenpox)	If you have not had chickenpox (varicella), if you haven't had varicella vaccine, or if you don't have an up-to-date blood test that shows you are immune to varicella (i.e., no serologic evidence of immunity or prior vaccination) get 2 doses of varicella vaccine, 4 weeks apart.
Tdap (Tetanus, Diphtheria, Pertussis)	Get a one-time dose of Tdap as soon as possible if you have not received Tdap previously (regardless of when previous dose of Td was received). Get Td boosters every 10 years thereafter. Pregnant HCWs need to get a dose of Tdap during each pregnancy.
Meningococcal	Those who are routinely exposed to isolates of N. meningitidis should get one dose.

Technicians: How to Help Your Pharmacist

- Review patient ages when they pick up prescriptions – and alert the pharmacist to opportunities to immunize (e.g. zoster and pneumococcal)
- Alert the pharmacist when patient's conditions may warrant vaccination (many, many examples).
- Make positive statements to patients about vaccines.
- Ensure vaccines are stocked and available when patients need them – patients are unlikely to return.
- Set up re-call reminder systems to bring patients back for vaccines dosed in a series…and leverage across the health-system with other providers.
- Ensure your pharmacy is connected to the state's Immunization Information System (registry), and then use it!

Prevention of Influenza: Progress toward a Universal Vaccine

- Vaccination represents the primary strategy to reduce the morbidity and mortality associated with influenza infection
- Currently, annual vaccination is required with seasonal influenza vaccine products
- Research has been underway for several years to identify a longer-lasting vaccine candidate
- Several approaches have been explored by the National Institute of Allergy and Infectious Diseases (NIAID)
- In May 2018, enrollment began in a Phase 2 study for a universal vaccine

Dennis' Broccoli Stalk (or Stem) and Head Analogy for the Influenza Virus

Universal Influenza Vaccine Concepts

- The hemagglutinin protein on the outer surface of the influenza virus consists of a stem and a head
- The head region varies from season to season and is the target of current seasonal influenza vaccine
- The stem (stalk) region of the protein remains relatively unchanged and is a current target of research for a universal longer acting vaccine

https://images.slideplayer.com/24/6946434/slides/slide_14.jpg

Universal Influenza Vaccine Efforts

- A NIAID research focus is to develop an influenza vaccine that provides robust, long-lasting protection against multiple subtypes of influenza virus, which could eliminate the need for annual vaccination with a seasonal influenza vaccine
- According to NIAID, a universal vaccine should:
  - Be at least 75% effective
  - Protect against multiple strains of influenza virus
  - Provide protection that lasts at least one year
  - Be suitable for people of all ages

Erbelding EJ, et al. JID 2018;218: 347-354

- Other Strategies for Managing and Preventing Influenza

Influenza Illness

- Uncomplicated: abrupt onset
  - Fever
  - Myalgia
  - Headache
  - Malaise
  - Cough
  - Sore throat
  - Rhinitis
- Typically resolves in 3 to 7 days with lingering cough and malaise

- Complications:
- Viral pneumonia
- Secondary bacterial pneumonia
- URT infections
- Sepsis
- Febrile seizures
- Less common: encephalopathy, myocarditis, myositis, Reye's syndrome
- Populations at higher risk include young, elderly, and people with cardiac or pulmonary diseases

Laboratory Diagnosis

- Surveillance and diagnostic testing can aid clinical judgment/guide treatment
- 60-69% practitioners report testing
- Diagnosis tests include viral culture, serology, rapid antigen, RT-PCR, and immunofluorescence assays
- Selected rapid influenza diagnostic tests (RIDTs) approved in outpatient settings
  - Others require moderate complex lab

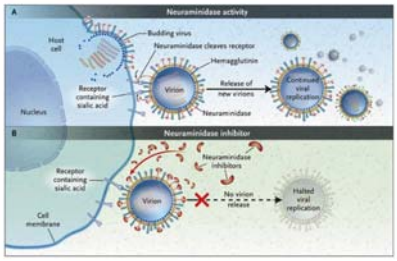
MMWR 2011 (Jan 21); 60 (1): No. RR-8

Influenza Antiviral Agents for Treatment and Prevention of Influenza

- Neuraminidase inhibitors – active against Influenza A and B
  - Oseltamivir – oral (Tamiflu or generic)
  - Zanamivir – inhaled (Relenza)
  - Peramivir – intravenous (Rapivab)
- Adamantanes – not currently recommended for use due to resistance risk of >99%
  - Amantadine
  - Rimantadine

www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Neuraminidase Inhibitors Mechanism of Action



From Moscona A. N Engl J Med 2005; 353: 1363-73.

Antiviral Agent	Treatment or Prophylaxis	Eligible Patient Age	Not Recommended In	Common Adverse Reactions Reported
Oseltamivir (oral)	Both	Tx: any age PPx: 3 months or older		Nausea, vomiting, headache. Some reports of dermatologic reactions and neuropsychiatric events
Zanamivir (Inhaled)	Both	Tx: 7 years and older PPx: 5 years and older	Underlying respiratory disease (e.g., asthma or COPD); or hospitalized patients	Oropharyngeal or facial edema, skin rash, bronchospasm, sinusitis, dizziness. Some reports of neuropsychiatric events
Peramivir (Intravenous)	Treatment	2 years and older		Diarrhea. Some reports of dermatologic reactions and neuropsychiatric events

www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Treatment with Antiviral Therapies

- Initiate as soon as possible when influenza is suspected or confirmed and patient: (preferred within 48 hours of illness onset)
  - Is hospitalized
  - Has severe, complicated or progressive disease
  - Is at higher risk for complications
- High risk include young (less than 2 years), 65 years and older, immunosuppressed, or chronic pulmonary, cardiac, renal, hepatic, metabolic, or neurologic disorders
- High risk also includes pregnancy, American Indians, and residents in LTC
- Can be used in previously healthy, symptomatic outpatients, based on clinical judgement if within 48 hours of onset of symptoms
- Do not wait for laboratory confirmation to start therapy
- Treatment duration is 5 days for oral and inhaled therapy and one day for IV

MMWR 2011; 60(1): 1-25

Treatment with Antiviral Therapies

- Antivirals reduce symptoms by ~ 1 day if started within 48 hours of onset
- Reduces complications of pneumonia and death
- Treatment indicated for
  - People at risk for complications
  - People with moderate to severe disease
  - LTC residents who are ill during outbreak

MMWR 2011; 60(1): 1-25

Antiviral Agent	Use and Duration	Child Dose	Adult Dose
Oseltamivir	Treatment (5 days)	<1 year old: 3mg/kg/dose twice daily One year or older: Weight based dosing ranging from 30 mg – 75 mg twice daily	75 mg twice daily
	Prophylaxis (7 days)	3 M-1 year: 3 mg/kg once daily One year and older: Weight based dosing ranging from 30 – 75 mg once daily	75 mg once daily
Zanamivir	Treatment (5 days)	7 years and older: 10 mg inhaled twice daily	10 mg (2 inhalations) twice daily
	Prophylaxis (7 days)	5 years and older: 10 mg inhaled once daily	10 mg (2 inhalations) once daily
Peramivir	Treatment (1 day)	2 to 12 years: 12 mg/kg/dose up to 600 mg once	600 mg once by IV infusion over at least 15 minutes (over 13 years of age)

Longer treatment durations may be used based on severity;
Oseltamivir and Peramivir are dose-adjusted in renal dysfunction

MMWR 2011; 60(1): 1-25

Pre and Post Exposure Prophylaxis with Antiviral Therapies

- Although antivirals are 70 to 90% effective in preventing influenza illness when used prophylactically, their use is not routinely recommended, except in institutional outbreaks (e.g., LTC facilities)
- When prophylaxis is used for known exposure, should be started within 48 hours
- Consideration can be given to:
  - People at high risk for complications who received influenza vaccine within the past two weeks (or not at all)
  - People with immunocompromising conditions or on immunosuppressive therapies
- Duration for known exposure is 1 week; with outbreak, duration is at least 2 weeks, and one week longer than last documented case

www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Drug-Specific Considerations

- Can be used in pregnancy (but Category C)
- For decreased renal function (CrCl 10-30) reduce oseltamivir by half for both Tx and prophylaxis
- Safety
  - Zanamivir-avoided in respiratory/cardiac disease
  - Oseltamivir- GI in 10%; Neuropsychiatric events reported
- Drug interactions not a major concern

MMWR 2011 (Jan 21); 60 (1): No. RR-8

Renal Dosing Adjustment Recommendations from CDC

Antiviral Agent	CrCl Estimate	Treatment Dose	Prophylaxis Dose
Oseltamivir	61 to 90 ml/min	75 mg twice daily	75 mg once daily
	31 to 60 ml/min	30 mg twice daily	30 mg once daily
	11 to 30 ml/min	30 mg once daily	30 mg every other day
	Dialysis	30 mg after dialysis session (varies)	30 mg weekly after dialysis (varies)
Peramivir	Greater than 50 ml/min	600 mg once	
	30 to 49 ml/min	200 mg once	
	10 to 29 ml/min	100 mg once	
	Dialysis	Based on CrCl	

www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Case Scenario: Acute Influenza

- Review Sally Smith case
- SS is a 73 year old woman with new onset of fever, muscle aches and respiratory symptoms
- On presentation, she is mildly dehydrated and hypoxemia
- She is admitted for fluids and observation

At your Table, Discuss:

- What pharmacotherapy recommendations do you have for Sally Smith
  - When should it be started, if at all?
  - What regimen is appropriate?
  - What are the goals for her management?
- Should this patient receive an influenza vaccine now?
- Assuming that her children and grandchildren are healthy and without symptoms, what should be recommended?

Select groups for report

Should Sally Smith receive an influenza vaccine now?

A. Yes, at discharge
B. Yes, at least 48 hours after completing antiviral therapy
C. No, not until next year

Summary

- An annual epidemic of influenza occurs annually and is associated with excess morbidity and mortality
- Currently, annual vaccination with seasonal influenza vaccine is the primary strategy to reduce problems associated with influenza
- Proper storage, handling, and administration of influenza vaccine is imperative to ensure that maximum effectiveness is achieved
- Health care personnel can educate, advocate, and provide vaccination services to reduce the risk and complications associated with influenza
- Antiviral therapies have a role when acute influenza infection is present or during outbreaks

The Flu Stops Here: Enabling Pharmacists and Pharmacy Technicians to Join the Fight
Illinois Council of Health System Pharmacists
September 14, 2018

Scenario One: Impact of Influenza Illness

Ann is 53 years old with Type 2 Diabetes and chronic lung disease (previously a smoker)

- Admitted to hospital with influenza, transferred to ICU and required intubation.
- Prior to influenza illness, diabetes and lung disease were well controlled and stable on medications.
- During ICU stay, experienced acute confusion for 2 days.
- Upon discharge home, experienced permanent loss of independence in activities of daily living due to physical limitations as a result of influenza.
- She had not been vaccinated in the current season, nor had anyone in her household.

Scenario Two: Vaccine Inventory

You are in charge of inventory management for both inpatient and outpatient services in your health system. The infection control committee has decided to intensify its efforts to prevent influenza infection through vaccination of staff and patients. They've asked the pharmacy department to ensure adequate supply for a) inpatient utilization, b) staff immunization, and c) outpatient clinic and pharmacy utilization.

Scenario Three: Acute influenza infection

CC: "I just don't feel well. I am so tired and my whole body aches. I keep having chills and I had a fever this morning"

HPI: Sally Smith is a 73 year old female who presented to her primary care physician with complaints of increasing fatigue and generalized muscle ache for the past 24 hours. She states that she stared with a sore throat, cough and runny nose two days prior. Her worsening symptoms prompted her to come to the clinic today.

ROS: General symptoms as noted above. Patient also endorses intermittent nausea, and she experienced diarrhea earlier today

PMH: Patient has a relatively unremarkable medical history except for hypertension and nasal allergies which began about 10 years ago.

SH and FH: Ms. Smith is a widow for 10 years. She lives with her son and family which includes two granddaughters, ages 18 months and 4 years. Family history is positive for breast cancer (mother) and hypertension (mother and siblings). She denies alcohol or illicit drug use, and stopped smoking 8 years ago (40 pack year history).

Meds: Amlodipine 10 mg daily; fluticasone nasal spray 50 mcg, each nostril daily.

Vaccines: Tdap 4 years ago, no vaccines since because of a concern for safety and fear of needles.

Allergies/ADR: ACE-I caused rise in creatinine, NKDA

PE: Hgt 68 inches, Wgt 64 kg, T: 38.5C BP 116/72, P 90, RR 19, O_2 sat 91%. Her skin is warm and mucous membranes are dry. A focused exam of her heart and abdomen was unremarkable. Lungs revealed crackles which cleared with coughing. She is A&O x3.

Labs: serum chemistry and hematology pending; one month ago, a baseline SCr was 1.5. A chest radiograph is unremarkable except for bibasilar atelectasis. Respiratory viral panel is also pending.

Assessment: possible influenza syndrome

Plan: Based on patient's hydration status and hypoxemia, will admit for fluids and observation while awaiting laboratory results.