Influenza Vaccines for Older Adults

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Advisory Committee on Immunization Practices (ACIP)
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Acknowledgements

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Overview

- Burden of influenza among older adults (ages 65 years and older).
- Influenza vaccine efficacy/effectiveness among older adults.
- Challenges in comparing influenza vaccines.
- Systematic review—overview of retrieved literature.

Burden of Influenza Among Older Adults

Surgeon General's Recommendation for Influenza Immunization—United States, 1960

Burney LE, Public Health Reports, October 1960, Vol. 75(10), page 944.

The high-risk groups who contribute most to the excess deaths and who the Public Health Service believes should be routinely immunized each year are:

1. Persons of all ages who suffer from chronic debilitating disease, in particular: (*a*) rheumatic heart disease, especially mitral stenosis; (*b*) other cardiovascular diseases, such as arteriosclerotic heart disease or hypertension—especially patients with evidence of frank or incipient insufficiency; (*c*) chronic bronchopulmonary disease, for example, chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, or pulmonary tuberculosis; (*d*) diabetes mellitus; (*e*) Addison's disease.
2. Pregnant women.
3. All persons 65 years or older.

STATEMENT

By Leroy E. Burney, Surgeon General, Public Health Service

Influenza Immunization

Two outbreaks of influenza swept the United States in the fall of 1957 and the winter of 1958, resulting in 60,000 more deaths than would be expected under normal conditions. There were, in addition, more than 26,000 excess deaths during the first 3 months of 1960 which also were considered to be the result of influenza.

These departures from the usually predictable norms prompted the Surgeon General's Advisory Committee on Influenza Research to analyze the cause and to seek measures to prevent such an occurrence in the future.

The committee found that a new antigenic variant, the Asian strain, because of its widespread introduction and the general lack of resistance to it, was the direct cause of the excess number of deaths, not only in the total population but most markedly among the chronically ill, the aged, and pregnant women. As a result of these findings, the Public Health Service is urging a continuing program to protect these high-risk groups in order to prevent a recurrence of this excess mortality.

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2. Pregnant women.
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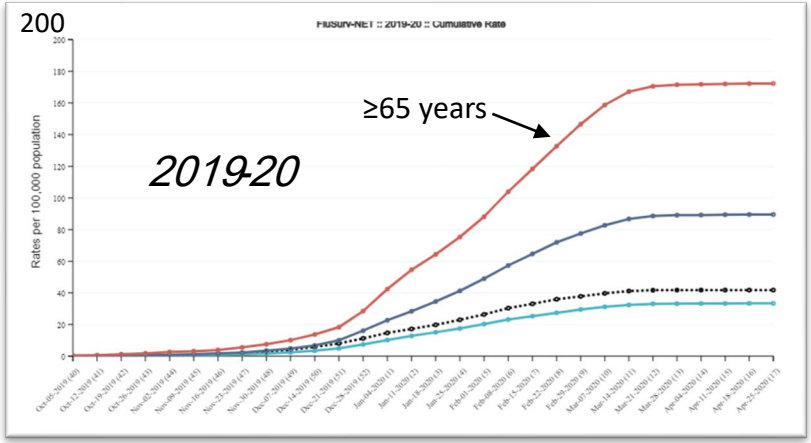
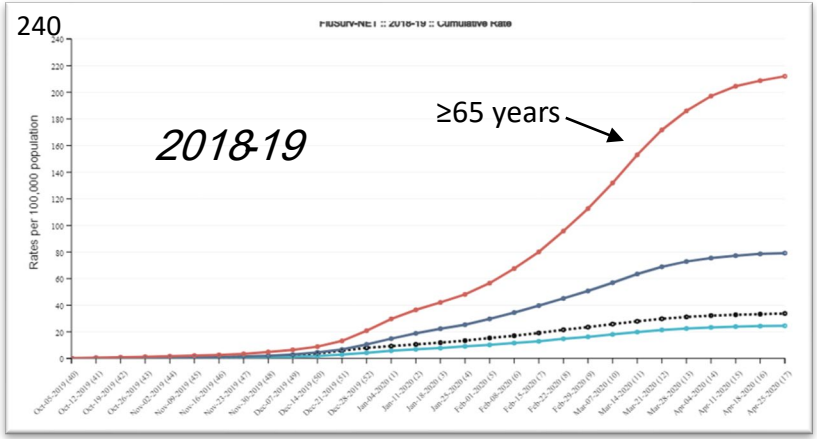
The adult dosage recommended by the advisory committee for initial immunization is 1.0 cc. (500 cca units) of polyvalent vaccine, administered subcutaneously on two occasions separated by two or more months. Preferably, the first dose would be given no later than September 1 and the second no later than November 1. Persons previously immunized with polyvalent vaccine should be reinoculated with a single booster dose of 1.0 cc. subcutaneously each fall, prior to November 1. The only contraindication to vaccination would be a history of food allergy to eggs or chicken or a prior history of allergic reaction to an egg-produced vaccine, such as the commercial influenza product.

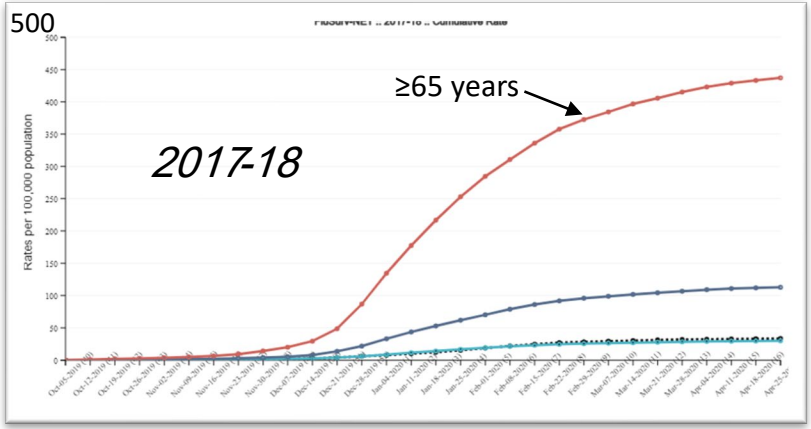
The time to start such a program is before the onset of the influenza season this fall. In the past, influenza vaccination has been sparse and sporadic, and primarily in response to an epidemic or the threat of an epidemic. The unpredictability of recurrence of influenza and its continued endemic occurrence are well known. Therefore, the Public Health Service strongly recommends that immunization of these high-risk groups be started now and continued annually, regardless of the predicted incidence of influenza for specific years.

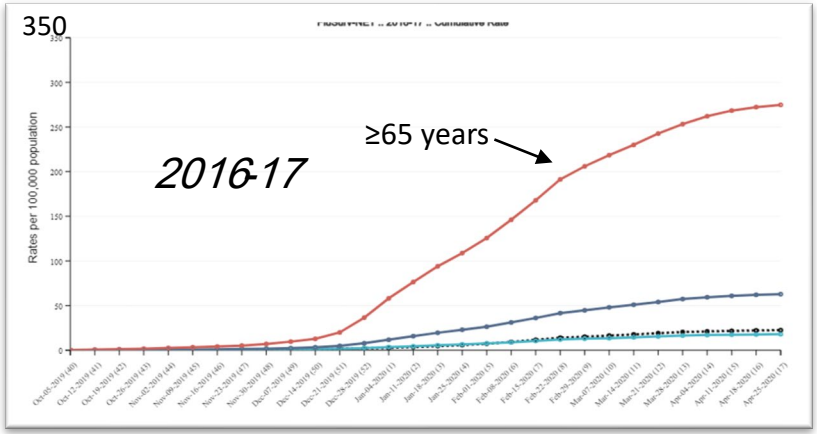
The members of the Surgeon General's Advisory Committee on Influenza Research are: Colin M. MacLeod, M.D., chairman, University of Pennsylvania, Fred M. Davenport, M.D., University of Michigan, Morris Schaeffer, M.D., bureau of laboratories of the City of New York Health Department, George Burch, M.D., Tulane University, Dorland J. Davis, M.D., National Institute of Allergy and Infectious Diseases, Public Health Service, Thomas F. Sellers, M.D., Georgia State Department of Health, and Glenn S. Usher, M.D., Communicable Disease Center, Public Health Service.

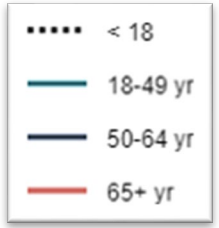
Cumulative Influenza Hospitalizations per 100,000 Population by MMWR Week—FluSurv-NET, 2016-17 through 2019-20 Seasons







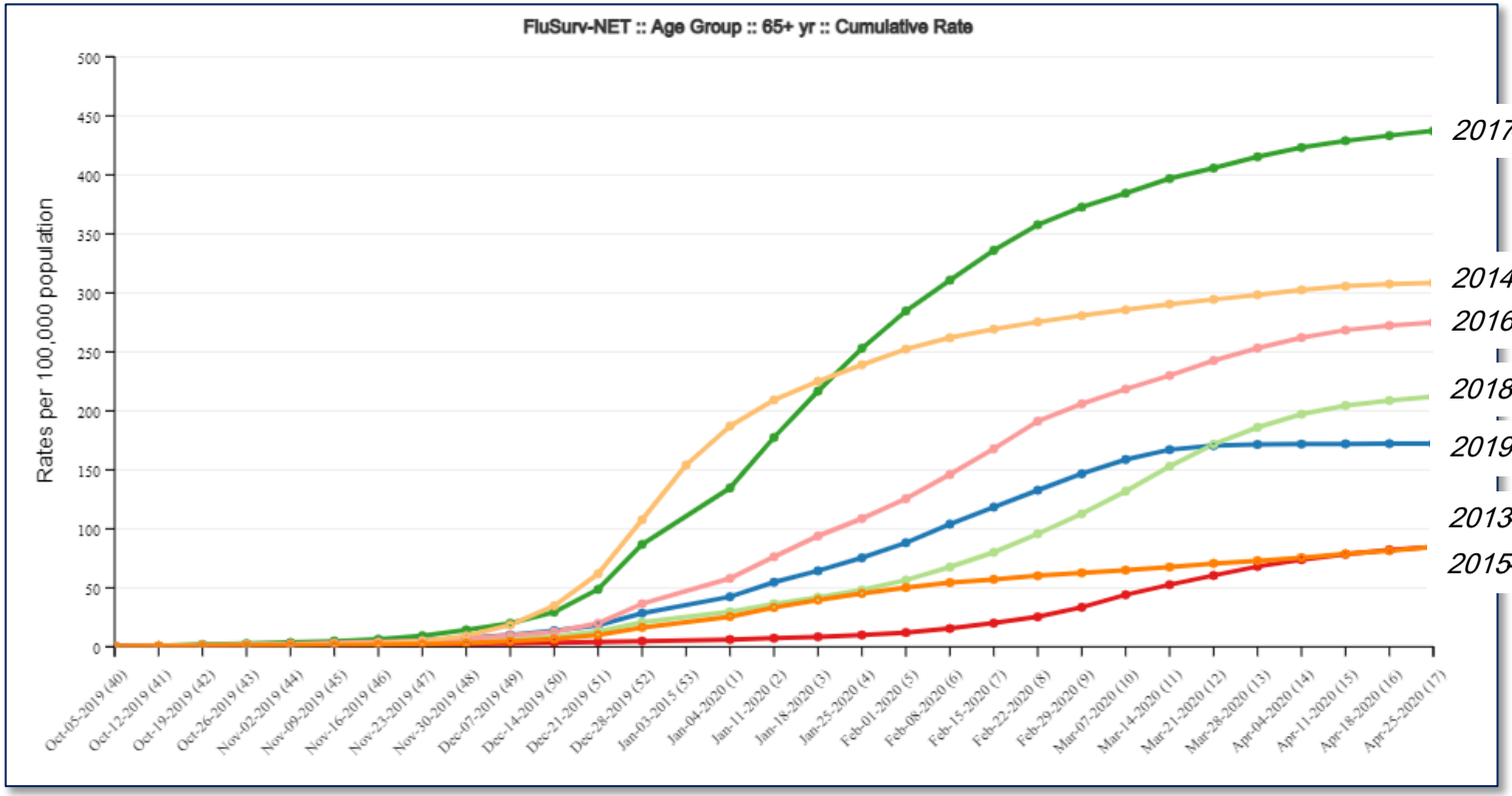




Source: CDC, FluSurv-NET (FluView Interactive)

Cumulative Influenza Hospitalizations per 100,000 Population by MMWR Week—FluSurv-NET

Ages ≥65yrs, H3N2- vs H1N1pdm09-predominant seasons



2017-18: H3N2, B/Yamagata

2014-15: H3N2, B/Yamagata

2016-17: H3N2, B/Yamagata

2018-19: early H1N1pdm09, late H3N2

2019-20: H1N1pdm09, B/Victoria

2013-14: H1N1pdm09

2015-16: H1N1pdm09, mixed B

Source: CDC FluSurv-NET (FluView Interactive)

Influenza Vaccine Efficacy/Effectiveness
Among Older Adults

Influenza Vaccine Effectiveness is Generally Lower Among Older Adults than Younger Age Groups

Season	Predominant viruse(s)	Overall VE, % (all ages, viruses, and vaccine types)	⩾65 yrs (all viruses and vaccine types)
2019-20	H1N1pdm09,B/Victoria	**39 (32, 44)**	**39 (9, 59)**
2018-19	early H1N1pdm09,late H3N2	**29 (21, 35)**	12 (-31,40)
2017-18	H3N2,B/Yamagata	**38 (31, 43)**	17 (-14,39)
2016-17	H3N2,B/Yamagata	**40 (32, 46)**	20 (-11,43)
2015-16	H1N1pdm09,mixed B	**48 (43 55)**	**42 (6, 64)**
2014-15	H3N2,B/Yamagata	**19 (10, 27)**	**32 (3, 52)**
2013-14	H1N1pdm09	**52 (44, 59)**	**50 (16, 71)**
2012-13	H3N2	**49 (43, 55)**	26 (-10,50)
2011-12	H3N2,mixed B	**47 (36, 56)**	43 (-18,72)

Source:
CDC, U.S. Flu VE Network, https://www.cdc.gov/flu/vaccinework/past-seasonsestimates.html

Influenza Vaccines by Age Indication—United States, 2021–22 Influenza Season

Vaccine type		0 through 6 mos	6 through 23 mos	2 through 17 yrs	18 through 49 yrs	50 through 64 yrs	≥65 yrs
IIV4s	Standard-dose, unadjuvanted inactivated (IIV4)		Afluria Quadrivalent Fluarix Quadrivalent FluLaval Quadrivalent Fluzone Quadrivalent				
	Cell culture-based inactivated (ccIIV4)		Flucelvax Quadrivalent				
	Adjuvanted inactivated (aIIV4)						Fluad Quadrivalent
	High-dose inactivated (HD-IIV4)						Fluzone High-Dose Quadrivalent
RIV4	Recombinant (RIV4)				Flublok Quadrivalent		
LAIV4	Live attenuated (LAIV4)			FluMist Quadrivalent			

IIV4=quadrivalent inactivated influenza vaccine, *RIV4*=quadrivalent recombinant influenza vaccine, *LAIV4*=quadrivalent live attenuated influenza vaccine, *mos*=months, *yrs*=years

Not approved for age group *Egg-based* *Not egg-based*

High-dose Inactivated Influenza Vaccine:

HD-IIV3 (Fluzone High-Dose) and HD-IIV4 (Fluzone High-Dose Quadrivalent)

- HD-IIV3 approved in 2009; replaced with HD-IIV4 in 2020-21 .
- Contains four times the quantity of hemagglutinin per vaccine virus compared with standard-dose inactivated vaccines (60 µg vs. 15 µg).
- HD-IIV3 demonstrated superior efficacy to standard-dose Fluzone in a randomized trial conducted among 32,000 participants ages ≥65 years over 2011-12 and 2012-13 seasons.
- HD-IIV4 demonstrated noninferior immunogenicity to HD-IIV3 for the three viruses common to both vaccines, and superior immunogenicity to the additional influenza B viruses not present in the trivalent comparators.

MF59-Adjuvanted Inactivated Influenza Vaccine:
aIIV3 (Fluad) and aIIV4 (Fluad Quadrivalent)

- aIIV3 approved in the US in 2016; in use in Europe as early as 1997.
- aIIV4 approved in 2020; quadrivalent is available as of 2020-21.
- Contains the lipid-in water adjuvant, MF59.
- Quadrivalent (aIIV4) demonstrated favorable safety compared with Tdap in a randomized trial of 6,740 persons ages ≥65 years over two seasons (Northern hemisphere 2016-17 and Southern Hemisphere 2017).
  - Primary efficacy endpoints were not met (88% of viruses from culture-confirmed influenza cases in the aIIV4 arm were antigenically mismatched).
  - Efficacy higher against illness defined by higher fever.

Recombinant Influenza Vaccine:

RIV3 (Flublok) and RIV4 (Flublok Quadrivalent)

- RIV3 approved in 2013; RIV4 approved in 2017.
- Only RIV4 available since 2018-19.
- Contains 45 µg/virus recombinant hemagglutinin (no viruses or eggs used).
- RIV4 demonstrated efficacy relative to SD-IIV4 in a randomized study conducted among ~8600 persons ages ≥50 years over one season (2014-15).

ACIP Recommendations Concerning Influenza Vaccines for Older Adults

- Provide descriptive summary of efficacy and effectiveness data.
  - There are studies supporting relative benefits for each; number, size, and designs vary.
  - Comparisons among these three vaccines against lab-confirmed outcomes are limited.
  - Most accumulated evidence focuses on HD-IIV3 and aIIV3 (which are now exclusively available as quadrivalent formulations).
- No preference is expressed for any one vaccine over another; any IIV or RIV is appropriate.
- Vaccination should not be delayed to find a specific vaccine when an appropriate one is available.

Challenges in Comparing Influenza Vaccines

Influenza Vaccine Efficacy and Effectiveness (VE) Vary

- Viral factors:
  - Circulating virus types and subtypes
  - Constant mutations and varying degree of match each season
  - Neither of these can be predicted ahead of the season

- Host factors:
  - Age/immunosenesence
  - Chronic medical conditions
  - Past influenza illnesses/exposures
  - Previous vaccination history

Relative VE (rVE) of Influenza Vaccines Compared to One Another Varie

- Izurieta et al analyses of CMS data
  - 12-13 million people aged ≥65 years each season.
  - Analyses comparing multiple vaccine types.
  - VE against influenza-associated hospital encounters (inpatient stays and ER visits), defined by ICD influenza codes.

	Relative VE compared with egg-based SD-IIV4		
Vaccine	**2017-18**	**2018-19**	**2019-20**
HD-IIV3	**9.0 (7.2, 10.6)**	**4.9 (1.7, 8.1)**	**6.8 (3.3, 10.1)**
aIIV3	**3.9 (1.4, 6.3)**	**7.7 (3.9, 11.4)**	**8.2 (4.2, 12.0)**
RIV4	-	-	**13.3 (7.4, 18.9)**
ccIIV4	**11.0 (7.9, 14.0)**	0.8 (-4.6,5.9)	2.8 (-2.8,8.2)

Izurieta et al: JID 2019;220:1955-1964
JID 2020;222:278-287
CID 2021;73(11):e4251-e4259

Considerations when Reviewing Literature

- Data from one/a few seasons might not generalize to all/most seasons.
- Ideally, preference for data from high-quality, randomized studies conducted over as many seasons as possible.
- Common study designs are associated with tradeoffs:

Randomized studies

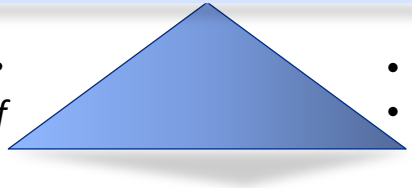
- *Less subject to bias →Higher quality data*
- *Vaccines of interest not constrained by uptake*

- *Less feasible to conduct over successive seasons (and very affected by degree of match in selected seasons)*

Observational Studies

- *More feasible to conduct over successive seasons using similar methods*

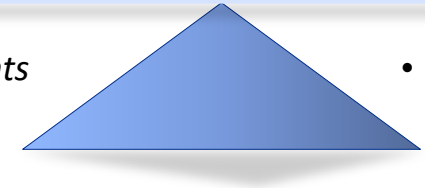
- *More subject to bias →Lesser quality data*
- *Vaccines of interest constrained by uptake*



Considerations when Reviewing Literature

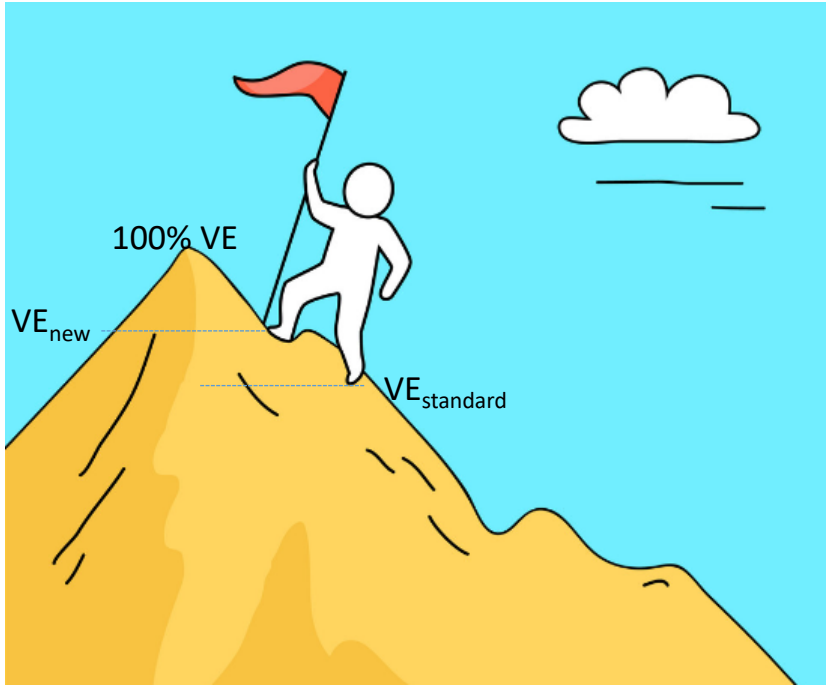
- If observational data are also to be considered,
  - More variability in study designs.
  - Differences in outcome definitions and analytic methods.
- Some tradeoffs with main observational designs:

Case-control studies	***Retrospective Cohort Studies***
• *Often lab-confirmed outcomes (more specific)*	• *Potentially very large sample sizes (e .g., tens of thousands to millions)*
• *Often smaller sample sizes/event counts (e.g., hundreds to thousands)*	• *Often diagnostic code-defined outcomes (less specific; potential for misclassification and bias)*

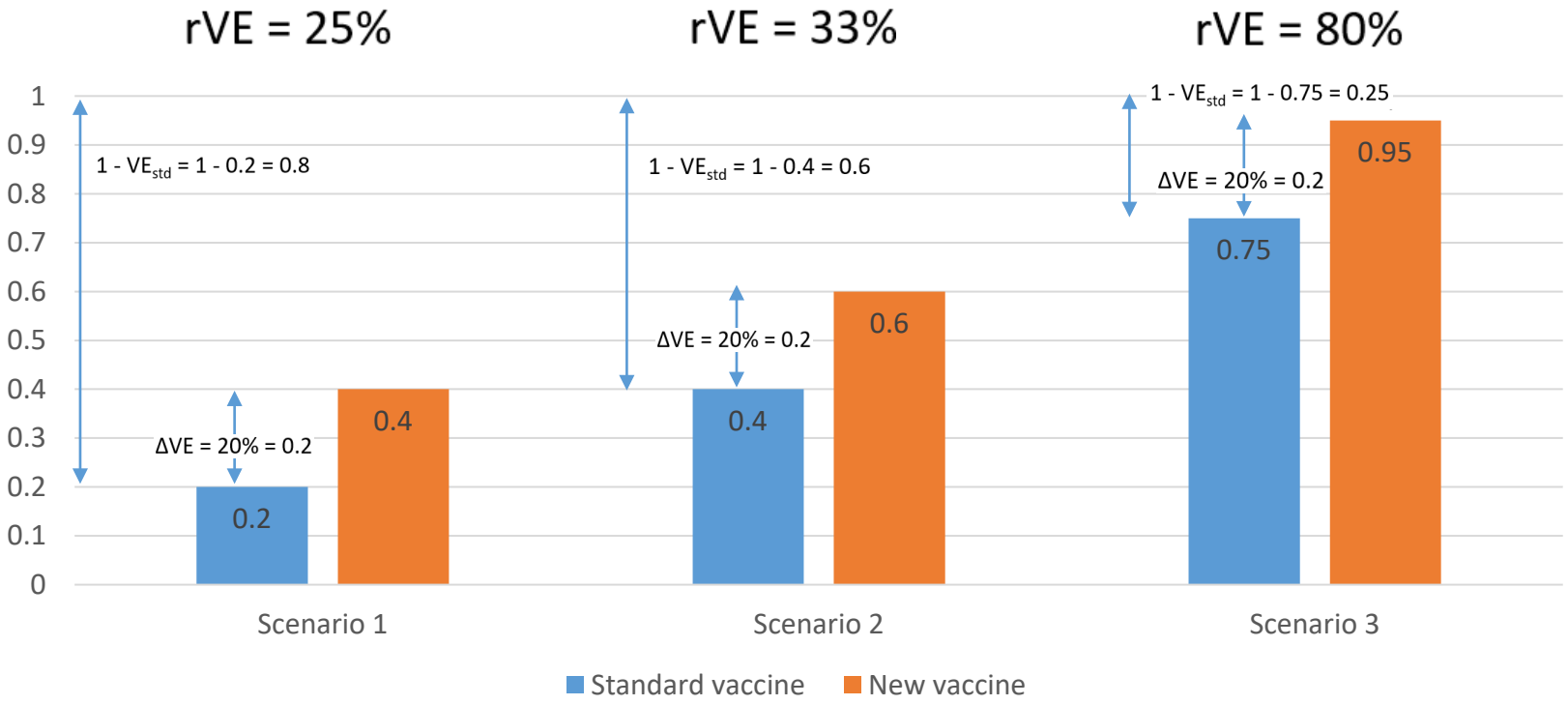


Considerations Regarding Relative VE

$$\text{Relative VE} = \frac{VE_{new} - VE_{standard}}{1 - VE_{standard}} * 100\%$$



Slide courtesy of Dr. Jill Ferdinands



Slide courtesy of Dr. Jill Ferdinands

Example: New vaccine VE for Ranges of Standard Vaccine VE and Relative

Standard vaccine VE	Relative VE	New vaccine VE	Absolute difference
20%	10%	28%	8%
20%	20%	36%	16%
20%	30%	44%	24%
30%	10%	37%	7%
30%	20%	44%	14%
30%	30%	51%	21%
40%	10%	46%	6%
40%	20%	52%	12%
40%	30%	58%	18%

Considerations for Relative VE When Baseline VE Varies

- The higher the effectiveness of the standard (comparator) vaccine, the higher the relative VE, for the same increase in absolute VE (i.e., the size of the relative VE depends on where you're starting from)
- Difficult to compare relative VE from different seasons when VE of comparator vaccine varies by season

Slide courtesy of Dr. Jill Ferdinands

Systematic Review of Influenza Vaccines for Older Adults

Overview of Retrieved Literature

Review Team:	Elif Alyanak
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Consultant:	Rebecca Morgan

Question

Whether the relative benefits and harms of HD-IIV, aIIV, and RIV, as compared with one another and with other influenza vaccines, favor the use of any one or more of these vaccines over other age-appropriate influenza vaccines for persons ≥65 years of age.

PICO—Population, Interventions, Comparators

Population:

- Adults aged ≥65 years

Interventions:

- Trivalent/quadrivalent high dose IIV, adjuvanted IIV, or RIV (U.S.-licensed, or similar in formulation/manufacture to U.S.-licensed)

Comparators:

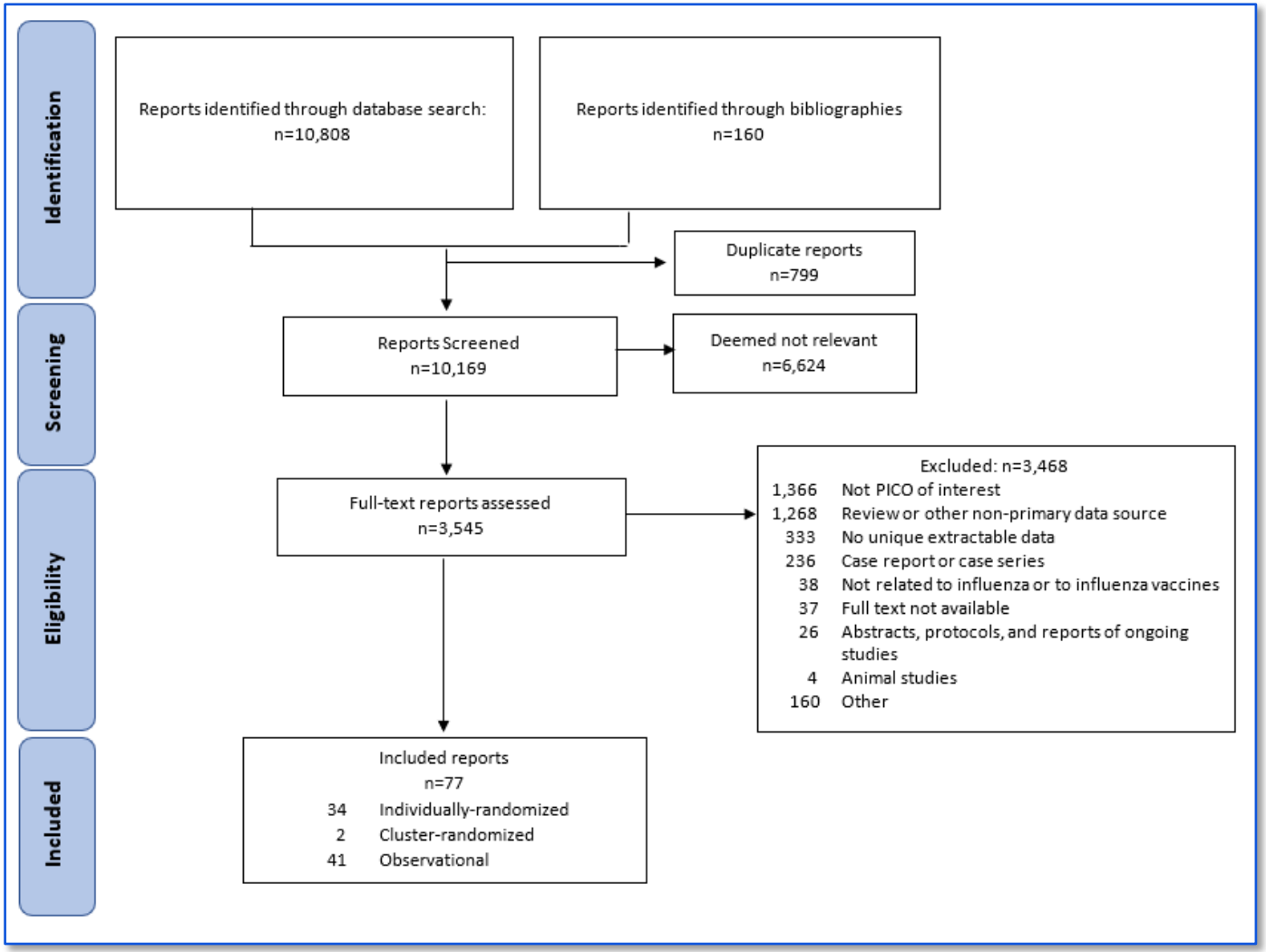
- Other trivalent or quadrivalent influenza vaccine (U.S.-licensed, or similar in formulation/manufacture to U.S.-licensed)
- Non-influenza control vaccine
- Placebo
- No vaccine

PICO—Outcomes

Primary Outcomes:

- Efficacy/Effectiveness (all viral types and subtypes)
  - Influenza illness
  - Influenza-associated outpatient/emergency visits
  - Influenza-associated hospitalizations
  - Influenza-associated deaths
- Safety
  - Any solicited systemic adverse event (grade ≥3)
  - Any solicited injection site adverse event (grade ≥3)
  - Any serious adverse event (SAE)
  - Guillain-Barre syndrome

PRISMA Diagram



Randomized Studies

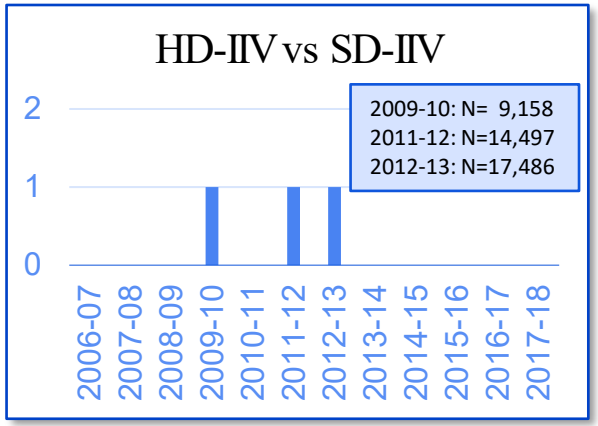
Efficacy Outcomes

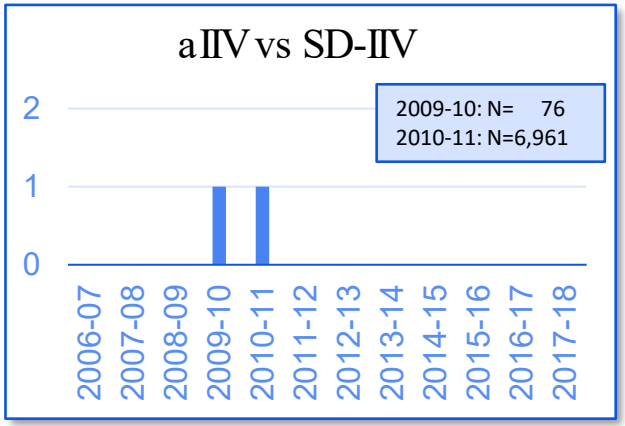
Randomized Studies Overview—Number of Studies by Efficacy Outcome

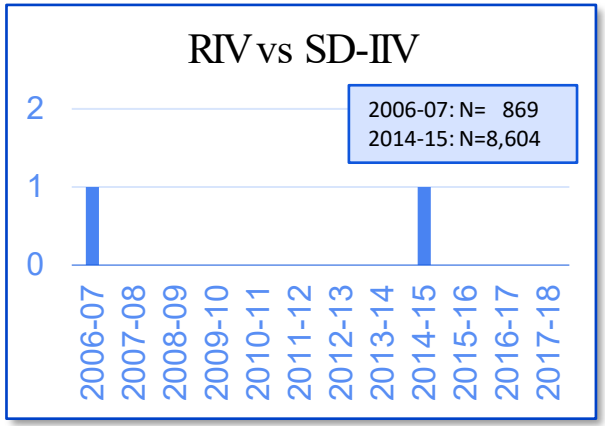
Comparison	Illnesses (all types/subtypes)	Medical visits (all types/subtypes)	Hospitalizations (all types/subtypes)	Deaths (all types/subtypes)
HD-IIV vs Standard-Dose Inactivated Comparator Vaccines (SD-IIV3 or SD-IIV4)				
HD-IIV3 vs SD-IIV3	2		2 (1 cluster randomized)	
HD-IIV3 vs SD-IIV4			1	
aIIV vs Standard-Dose Inactivated Comparator Vaccines (SD-IIV3 or SD-IIV4)				
aIIV3 vs SD-IIV3	2			
RIV vs Standard-Dose Inactivated Comparator Vaccines (SD-IIV3 or SD-IIV4)				
RIV3 vs SD-IIV3	1		1 (cluster randomized)	
RIV4 vs SD-IIV4	1			
HD-IIV, aIIV, and RIV vs one another				
HD-IIV3 vs aIIV3	1			
HD-IIV3 vs RIV4	1			
aIIV3 vs RIV4	1			
HD-IIV, aIIV, and RIV vs no vaccine, placebo, or noninfluenza control vaccine				
aIIV4 vs Tdap	1			

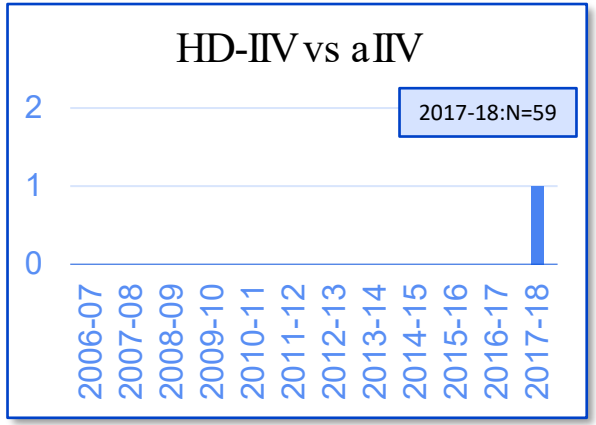
Influenza Illness— Individually-Randomized Studies—Lab-confirmed Outcomes

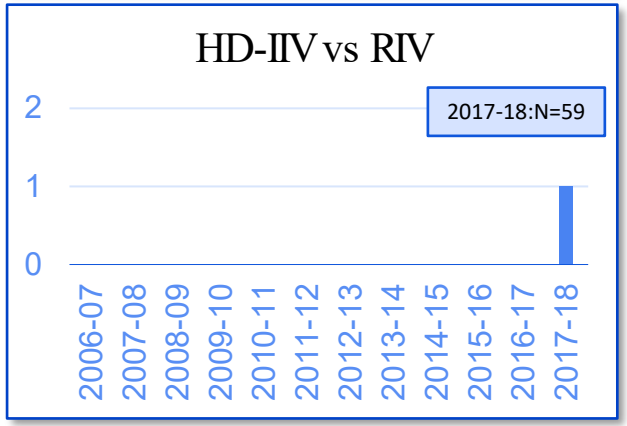
Number of Studies (y-axis) and Total Participants (boxes) by Season (x-axis)

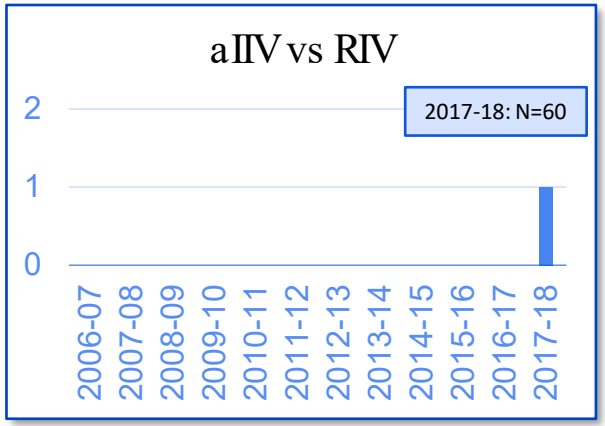












Influenza Illness– Individually-Randomized Studies

HD-IIV vs. SD-IIV

Paper / Year	Season(s)	Comparison	N	Outcome(s)	Relative VE (95% CI)
DiazGranados 2013	2009-10	HD-IIV3 vs SD-IIV3	9,158	Protocol-defined ILI, PCR-or culture-confirmed	2009-10: 12.6 (-140.5, 65.8)*
DiazGranados 2014	2011-12 and 2012-13	HD-IIV3 vs SD-IIV3	31,989	PCR-or culture-confirmed ILI due to any viral type or subtype Protocol-defined ILI (primary)† Modified CDC-defined ILI†	2011-12: **45.31 (6.95, 68.60)** 2012-13: **20.74 (4.43, 34.33)** Both seasons: **24.2 (9.7, 36.5)** Both seasons: 20.6 (-4.6, 39.9)

* 2009 pandemic season--no cases were due to antigenically matched viruses.

† Protocol defined ILI: respiratory illness with sore throat, cough, sputum production, wheezing, or difficulty breathing, concurrent with one or more of the following: temperature >37.2°C, chills, tiredness, headaches, or myalgia.
Modified CDC ILI: respiratory illness with cough or sore throat, concurrent with a temperature above 37.2°C.

Influenza Illness– Individually-Randomized Studies

aIIV vs. SD-IIV

Paper / Year	Season(s)	Comparison	N	Outcome(s)	Relative VE (95% CI)
Song 2013	2009-10	aIIV3 vs SD-IIV3	76	ILI associated with influenza confirmed by virologic testing)*	No lab-confirmed influenza observed during follow-up. Denominators by group not provided.
Frey 2014	2010-11	aIIV3 vs SD-IIV3	6,961	ILI (symptom-defined; no lab confirmation)†	9 (-16, 29)

* Fever ≥ 38°C with accompanying respiratory symptoms (cough, sore throat, or coryza).
† Temperature ≥37.2°C or feverishness and at least two of the following: headache, myalgia, cough, or sore throat.

Influenza Illness– Individually-Randomized Studies

aIIV vs. Tdap

Paper / Year	Season(s)	Comparison	N	Outcome(s)	VE (95% CI)
Beran 2020	NH 2016-17 SH 2017	aIIV4 vs Tdap	6,740	PCR-confirmed ILI, due to any viral type or subtype	
				Protocol-defined ILI (primary)*	19.8 (-5.3, 38.9)
				Modified CDC-defined ILI*	**32.1 (10.2, 48.7)**

* Protocol-defined ILI: at least one respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing) concurrently with at least one systemic symptom (temperature >37.2°C, chills, tiredness, headache, or myalgia).
Modified CDC-defined ILI: fever (temperature >37.2°C) with cough or sore throat.

Influenza Illness– Individually-Randomized Studies

RIV vs. SD-IIV

Paper / Year	Season(s)	Comparison	N	Outcome(s)	Relative VE (95% CI)
Keitel 2009	2006-07	RIV3 vs SD-IIV3	869	ILI* associated culture-confirmed influenza	Not calculated RIV3: 1/436 (0.2%) SD-IIV3: 2/433 (0.5%)
Dunkle 2017	2014-15	RIV4 vs SD-IIV4	8,604	ILI† associated with PCR-confirmed influenza— Ages ≥50 years Ages ≥65 years	 **30 (10, 47)** 17 (-20, 43)

* Participants asked to present for illness evaluation if they recorded an influenza symptoms score of 2 or greater on the Flu Symptoms Card (based on presence of fever, cough, sore throat, and runny nose/stuffy nose, muscle or joint aches, headache, chills/sweats, and tiredness/malaise), or if they sought medical care for their acute illness.

† At least one symptom in both the respiratory and systemic illness categories, regardless of severity.

* Ages 50 years and older.

Influenza Illness — Individually-Randomized Studies

HD-IIV, aIIV, and RIV

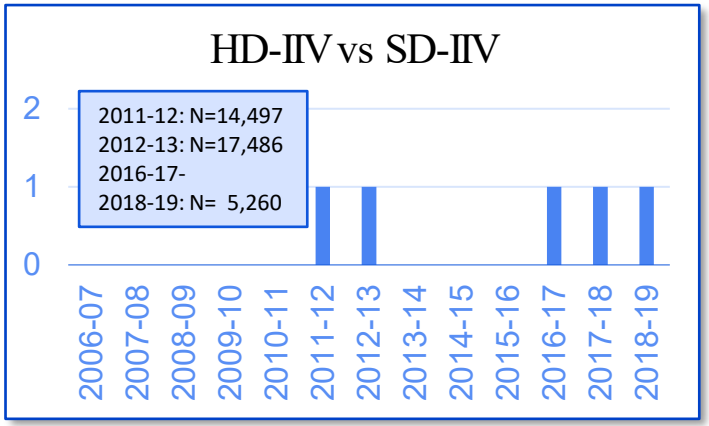
Paper / Year	Season(s)	Outcome	Vaccine	Instances of PCR-positive ILI/N (%)
Belongia 2020*	2017-18	PCR-confirmed influenza associated with respiratory illness†	HD-IIV3 aIIV3 RIV4	1/29 (3.3%) 3/29 (10%) 4/30 (13.3%)

* Ages 65 through 74.

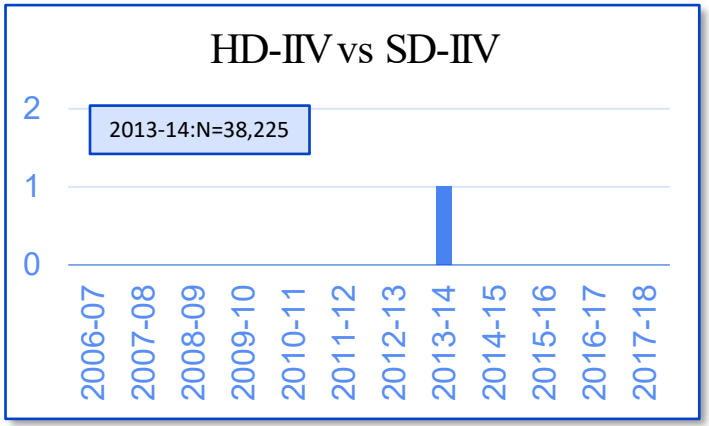
† Any two of the following seven symptoms: cough, fever/chills, stuffy/runny nose, headache, body aches/muscle aches, sore throat, shortness of breath, or fatigue

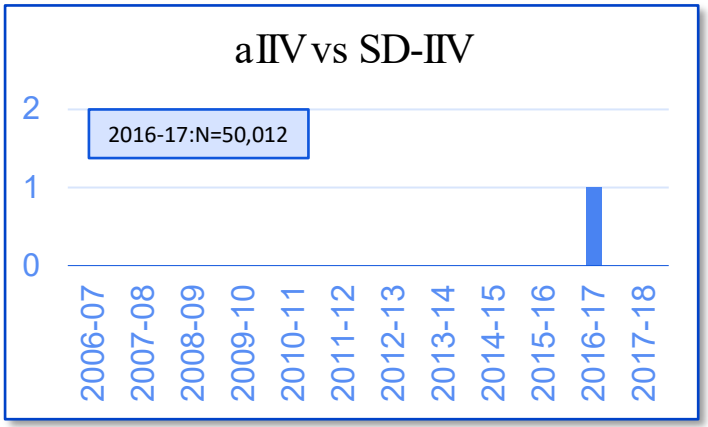
Influenza-associated Hospitalizations— Individually- and Cluster-Randomized Studies—Number of Studies (y-axis) and Total Participants (boxes) by Season (x-axis)

Individually-randomized studies



Cluster-randomized studies





Influenza -associated Hospitalizations —Individually-Randomized Studies

HD-IIV vs SD-IIV

Paper / Year	Season(s)	Comparison	N	Outcome(s)	Rate Ratio (95% CI)
DiazGranados 2015a	2011-12 and 2012-13	HD-IIV3 vs SD-IIV3	31,989	Serious adverse events (SAEs) fro DiazGranados 2014, adjudicated a possibly related to influenza	
				Influenza events	0.67 (0.19, 2.36)
				Pneumonia events	**0.60 (0.45, 0.81)**
				Asthma/Bronchial events	0.99 (0.72, 1.36)
				Other respiratory events	0.66 (0.42, 1.04)
Vardeny 2021	2016-17, 2017-18, and 2018-19	HD-IIV3 vs SD-IIV4	5,260 (median age 66-67 yrs, IQR 58-74)	Hospitalizations adjudicated as:	RR not calculated
				Primarily due to influenza	HD-IIV3 10/2630 (0.4%) SD-IIV4 8/2630 (0.3%) p=0.63
				Primarily due to pneumonia	HD-IIV3 47/2630 (0.2%) SD-IIV4 41/2630 (0.2%) p=0.56

Influenza -associated Hospitalizations — Cluster-Randomized Studies

HD-IIV vs SD-IIV

Paper / Year	Season(s)	Comparison	N	Outcome(s)	RR (95% CI)
Gravenstein 2017	2013-14	HD-IIV3 vs SD-IIV3	38,225	Pneumonia and influenza-coded hospitalizations	**RR: 0.79 (0.27, 0.95)**

aIIV vs SD-IIV

Paper / Year	Season(s)	Comparison	N	Outcome(s)	RR (95% CI)
McConeghy 2020	2016-17	aIIV3 vs SD-IIV3	50,012	Pneumonia and influenza-coded hospitalizations	**RR: 0.80 (0.66, 0.98)**

Randomized Studies—Efficacy Outcomes: Summary

- Data available comparing HD-IIV and RIV vs SD-IIVs against laboratory-confirmed outcomes.
- Limited comparison of aIIV vs SD-IIV against laboratory-confirmed influenza outcomes.
- Comparisons of HD-IIV, aIIV, and RIV with one another limited to one small study, as an exploratory endpoint.
- Within each vaccine comparison, limited number of seasons represented.
- Limited data on efficacy against severe influenza outcomes (e.g., hospitalization due to influenza);.
  - No data on laboratory-confirmed hospitalizations.
  - Estimates from individually randomized studies does not come from primary analyses.

Randomized Studies

Safety Outcomes

Randomized Studies Overview—Number of Studies by Safety Outcome

Comparison	Any injection site AE grade ≥3	Any solicited systemic AE grade ≥3	Any SAE	Guillain Barre syndrome
HD-IIV vs Standard-Dose Inactivated Comparator Vaccines				
HD-IIV3 vs SD-IIV3	2	2	6	1
HD-IIV3 vs SD-IIV4	1	1	2	1
aIIV vs Standard-Dose Inactivated Comparator Vaccines				
aIIV3 vs SD-IIV3	3	3	7	1
aIIV3 vs SD-IIV4	1	1	1	
RIV vs Standard-Dose Inactivated Comparator Vaccines				
RIV3 vs SD-IIV3	1	1	3	
RIV4 vs SD-IIV4	1	1	2	
HD-IIV, aIIV, and RIV vs one another				
HD-IIV3 vs aIIV3	2	2	2	1
HD-IIV3 vs RIV4	2	2	2	
aIIV3 vs RIV4	1	1	1	
HD-IIV, aIIV, and RIV vs no vaccine, placebo, or non-influenza control vaccine				
aIIV4 vs Tdap			1	

Any SAE—Individually Randomized Studies

HD-IIV vs SD-IIV

Paper / Year	Season(s)	Comparison	N	Events/n (%) HD-IIV		Events/n (%) SD-IIV	
DiazGranados 2013	2009-10	HD-IIV3 vs SD-IIV3	9158	408/6108	(6.7)	197/3050	(6.5)
DiazGranados 2014	2011-12 and 2012-13	HD-IIV3 vs SD-IIV3	31,983	1323/15990	(8.3)	1442/15993	(9.0)
Falsey 2009	2006-07	HD-IIV3 vs SD-IIV3	3,781	159/2541	(6.3)	93/1240	(7.5)
Keitel 2006	2001-02	HD-IIV3 vs SD-IIV3	101	3/50	(6.0)	3/51	(5.9)
Nace 2015	2011-12 and 2012-13	HD-IIV3 vs SD-IIV3	187	5/89	(5.6)	6/98	(6.1)
Tsang 2014	2007-08	HD-IIV3 vs SD-IIV3	639	16/320	(5.0)	21/319	(6.6)
Cowling 2020	2017-18	HD-IIV3 vs SD-IIV4	1,018	10/510	(2.0%)	13/508	(2.6%)
Vardeny 2021	2016-17, 2017-18, and 2018-19	HD-IIV3 vs SD-IIV4	5,210	2/2606	(0.08%)	4/2604	(0.2%)

Any SAE—Individually Randomized Studies

aIIV vs SD-IIV

Paper / Year	Season(s)	Comparison	N	Events/n (%) aIIV		Events/n (%) SD-IIV	
De Bruijn 2007	2004-05	aIIV3 vs SD-IIV3	259	1/130	(0.7%)	0/129	(0%)
De Donato 1999	1993-94 1994-95 1995-96	aIIV3 vs SD-IIV3	211*	5/248	(2.0%)	6/233	(2.6%)
Della Cioppa 2012	2008-09	aIIV3 vs SD-IIV3	91	0/47	(0%)	1/44	(2.3%)
Frey 2014	2010-11	aIIV3 vs SD-IIV3	7,082	248/3545	(7.0%)	247/3537	(7.0%)
Li 2008	2005-06	aIIV3 vs SD-IIV3	589	1/391	(0.2%)	0/198	(0%)
Scheifele 2013	2011-12	aIIV3 vs SD-IIV3	608	15/301	(5.0%)	13/307	(4.2%)
Sindoni 2009	2002-03	aIIV3 vs SD-IIV3	195	0/96	(0%)	0/99	(0%)
Cowling 2020	2017-18	aIIV3 vs SD-IIV4	1016	11/508	(2.1%)	13/508	(2.6%)

* Individuals (total 211) could be enrolled for more than one season and are counted separately for each season.

Any SAE—Individually Randomized Studies

RIV vs SD-IIV

Paper / Year	Season(s)	Comparison	N	Events/n (%) RIV		Events/n (%) SD-IIV	
Izikson 2015*	2012-13	RIV3 vs SD-IIV3	2,627	5/1314	(0.4%)	10/1313	(0.8%)
Keitel 2010	2006-2007	RIV3 vs SD-IIV3	869	36/436	(8.3%)	34/433	(7.9%)
Treanor 2006	Not noted	RIV3 vs SD-IIV3	199	1/100	(1.0%)	1/99	(1.0%)
Cowling 2020	2017-18	RIV4 vs SD-IIV4	843	4/335	(1.2%)	13/508	(2.6%)
Dunkle 2017*	2014-15	RIV4 vs SD-IIV4	8,672	145/4328	(3.4%)	132/4344	(3.0%)

* Ages 50 years and older.

Any SAE—Individually Randomized Studies

HD-IIV3 vs aIIV3

Paper / Year Published	Season(s)	Comparison	N	Events/n (%) HD-IIV		Events/n (%) aIIV	
Cowling 2020	2017-18	HD-IIV3 vs aIIV3	1018	10/510	(2.0%)	11/508	(2.2%)
Schmader 2021	2017-18, 2018-19	HD-IIV3 vs aIIV3	757	3/377	(0.8%)	9/378	(0.3%)

HD-IIV3 vs RIV4

Paper / Year	Season(s)	Comparison	N	Events/n (%) HD-IIV		Events/n (%) RIV	
Cowling 2020	2017-18	HD-IIV3 vs RIV4	845	10/510	(2.0%)	4/335	(1.2%)
Shinde 2020	2018-19	HD-IIV3 vs RIV4	304	6/153	(3.9%)	3/151	(2.0%)

aIIV3 vs RIV4

Paper / Year	Season(s)	Comparison	N	Events/n (%) aIIV		Events/n (%) RIV	
Cowling 2020	2017-18	aIIV3 vs RIV4	843	11/508	(2.2%)	4/335	(1.2%)

Randomized Studies—Safety Outcomes: Summary

- In general, no major imbalances in rates of SAEs
- For solicited adverse events, reporting across symptom categories i

Observational Studies

Overview—Number of Observational Studies by Outcome

Comparison	Illnesses	Outpatient/ ER visits	Hospitalizations	Inpatient/ Outpatient*	Inpatient/ ER*	Deaths	GBS
HD-IIV, aIIV, and RIV vs Standard-Dose Inactivated Comparator Vaccines							
HD-IIV3 vs SD-IIV3		4	4		4	1	
HD-IIV3 vs SD-IIV4		1	3		4		
HD-IIV3 vs SD-IIV unspecified		1	3	1	1	1	
aIIV3 vs SD-IIV3		4	2		3		1
aIIV3 vs SD-IIV4		2	3	2	5		
aIIV3 vs SD-IIV unspecified			2				
RIV3 vs SD-IIV3							1
RIV4 vs SD-IIV4			1				
HD-IIV, aIIV, and RIV vs one another							
HD-IIV3 vs aIIV3		3	4	2	6		
HD-IIV3 vs RIV4			1		1		
aIIV3 vs RIV4			1		1		

* Composite outcome

Outpatient-attended Illness— Observational Studies-Number of Studies by Season

Cohort studies (predominantly code -based outcome definitions)										
Comparison	1998-99	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19
HD-IIV vs SD-IIV				2	1		1		1	
aIIV vs SD-IIV	1								2	
RIV vs SD-IIV										
HD-IIV vs aIIV									2	1
HD-IIV vs RIV										
aIIV vs RIV										

Case-control studies (predominantly lab -confirmed outcome definitions)										
Comparison	1998-99	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19
HD-IIV vs SD-IIV							1	1	1	1
aIIV vs SD-IIV			1							
RIV vs SD-IIV										

Outpatient-attended Illness— Observational Studies-Number of Studies by Season

Arrows denote studies spanning multiple seasons

Cohort studies (predominantly code -based outcome definitions)

Comparison	1998-99	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19
HD-IIV vs SD-IIV				2	1		1		1	
aIIV vs SD-IIV	1								2	
RIV vs SD-IIV										
HD-IIV vs aIIV									2	1
HD-IIV vs RIV										
aIIV vs RIV										

Case-control studies (predominantly lab -confirmed outcome definitions)

Comparison	1998-99	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19
HD-IIV vs SD-IIV							1	1	1	1
aIIV vs SD-IIV			1							
RIV vs SD-IIV										

Hospitalizations— Observational Studies-Number of Studies by Season

Cohort studies (predominantly code -based outcome definitions)													
Comparison	2006-07	2007-08	2008-09	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19	2019-20
HD-IIV vs SD-IIV				1	2	3	3	3	2	1	2	1	1
aIIV vs SD-IIV					1	1	1	1	1	2	1	1	1
RIV vs SD-IIV													1
HD-IIV vs aIIV													
HD-IIV vs RIV													
aIIV vs RIV													

Case-control studies (predominantly lab -confirmed outcome definitions)													
Comparison	2006-07	2007-08	2008-09	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19	2019-20
HD-IIV vs SD-IIV									1	1			
aIIV vs SD-IIV													
RIV vs SD-IIV													

Hospitalizations— Observational Studies-Number of Studies by Season

Arrows denote studies spanning multiple seasons

Cohort studies (predominantly code -based outcome definitions)

Comparison	2006-07	2007-08	2008-09	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19	2019-20
HD-IIV vs SD-IIV				1	2	3	3	3	2	1	2	1	1
aIIV vs SD-IIV	1	1	1		1	1	1	1	1	2	1	1	1
RIV vs SD-IIV													1
HD-IIV vs aIIV													
HD-IIV vs RIV													
aIIV vs RIV													

Case-control studies (predominantly lab -confirmed outcome definitions)

Comparison	2006-07	2007-08	2008-09	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19	2019-20
HD-IIV vs SD-IIV									1	1			
aIIV vs SD-IIV													
RIV vs SD-IIV													

Outpatient -attended illnesses —Observational Studies

HD-IIVs vs SD-IIVs

Paper / Year	Season(s)	Design	Comparison	N	Outcome definition	Relative VE
Balasubramani 2020*	2015-16 through 2018-19	TNCC	HD-IIV3 vs SD-IIV	2,993	PCR-confirmed	**18 (0, 33)**
Izurieta 2015	2012-13	Retrospective cohort	HD-IIV3 vs SD-IIV3†	2,545,275	CPT for rapid test and Rx for oseltamivir	**21.9 (15, 28.7)**
Izurieta 2019	2017-18	Retrospective cohort	HD-IIV3 vs SD-IIV3†	9,482,899	CPT for rapid test and Rx for oseltamivir	-4.3 (-7.4,-1.3)
Izurieta 2019	2017-18	Retrospective cohort	HD-IIV3 vs SD-IIV4†	10,310,998	CPT for rapid test and Rx for oseltamivir	0.7 (-1.5, 2.9)
Shay 2017	2012-13 2013-14	Retrospective cohort	HD-IIV3 vs SD-IIV3	6,108,412	CPT for rapid test and Rx for oseltamivir	**15.3 (9.7, 20.6)**
Young-Xu 2018	2015-16	Retrospective cohort	HD-IIV3 vs SD-IIV3	230,741	ICD P&I codes	14 (-8, 32)

* Influenza A only.

†Comparison is vs egg-based SD-IIV

TNCC=test-negative case control

P&I=pneumonia and influenza

Outpatient -attended illnesses —Observational Studies

aIIVs vs SD-IIVs

Paper / Year	Season(s)	Design	Comparison	N	Outcome definition	Relative VE
Iob 2005	1998-99	Prospective cohort	aIIV3 vs SD-IIV3*	2,966	Symptomatic definition	**34 (18, 47)**
Izurieta 2019	2017-18	Retrospective cohort	aIIV3 vs SD-IIV3*	2,461,681	ICD influenza codes	-11.9 (-15.9, -8.1)
Izurieta 2019	2017-18	Retrospective cohort	aIIV3 vs SD-IIV4*	3,289,780	ICD influenza codes	-6.6 (-9.7, -3.5)
Pelton 2020	2017-18	Retrospective cohort	aIIV3 vs SD-IIV3*	340,804	CPT for rapid test and Rx for oseltamivir	**25 (17, 32.2)**
Pelton 2020	2017-18	Retrospective cohort	aIIV3 vs SD-IIV4*	446,600	CPT for rapid test and Rx for oseltamivir	**36.3 (31, 41.2)**
Van Buynder 2013	2011-12	TNCC	aIIV3 vs SD-IIV3	227	PCR-confirmed	**63 (4, 86)**

*Comparison is vs egg-based SD-IIV

Outpatient -attended illnesses —Observational Studies

HD-IIVs vs aIIVs

Paper / Year	Season(s)	Design	Comparison	N	Outcome(s)	rVE (95% CI)
Izurieta 2019	2017-18	Retrospective cohort	HD-IIV3 vs aIIV3	9,955,054	CPT for rapid test and Rx for oseltamivir	**6.8 (4.6, 8.9)**
Pelton 2020	2017-18	Retrospective cohort	HD-IIV3 vs aIIV3	1,504,168	CPT for rapid test and Rx for oseltamivir	**-19.9 (-28.2, -12.1)**
Pelton 2021	2018-19	Retrospective cohort	HD-IIV3 vs aIIV3	2,234,094	ICD influenza codes	**-7.1 (-11.5, 2.9)**

Hospitalizations —Observational Studies

HD-IIVs vs SD-IIVs

Paper / Year	Season(s)	Design	Comparison	N	Outcome definition	rVE (95% CI)
Doyle 2021	2015-16, 2016-17	TNCC	HD-IIV3 vs SD-IIV	1107	PCR-confirmed	27 (-1, 48)
Izurieta 2019	2017-18	Retrospective cohort	HD-IIV3 vs SD-IIV3*	9,482,899	ICD influenza codes	**12 (9.2, 14.8)**
Izurieta 2019	2017-18	Retrospective cohort	HD-IIV3 vs SD-IIV4*	10,310,998	ICD influenza codes	**10 (7.8, 12.3)**
Izurieta 2020	2018-19	Retrospective cohort	HD-IIV3 vs SD-IIV4*	9,450,592	ICD influenza codes	**5.2 (1.0, 9.3)**
Izurieta 2021	2019-20	Retrospective cohort	HD-IIV3 vs SD-IIV4*	8,757,884	ICD influenza codes	**6.9, (2.3. 11.4)**
Lu 2019	2012-13 2013-14 2014-15 2015-16 2016-17 2017-18	Retrospective cohort	HD-IIV3 vs SD-IIV	19,922,120	ICD influenza codes	**27.4 (20.2, 33.9)** 9.6 (-1.2, 19.3) **9.6 (5.2, 13.9)** 5.9 (-6.3, 16.8) **10.6 (1.9, 18.5)** 8.2 (-0.1, 15.9)
Richardson 2015	2010-11	Retrospective cohort	HD-IIV3 vs SD-IIV3	165,255	ICD P&I codes	≥65 yrs: 2 (-40, 32) **≥85 yrs: 48 (8, 71)**
Young-Xu 2018	2015-16	Retrospective cohort	HD-IIV3 vs SD-IIV3	2,410,208	ICD P&I codes	**25 (2, 43)**
Young-Xu 2019	2010-11--2014-15	Retrospective cohort	HD-IIV3 vs SD-IIV3	1,728,562	ICD P&I codes	**14 (6. 22)**

*Comparison is vs egg-based SD-IIV

P&I=pneumonia and influenza

Hospitalizations —Observational Studies

aIIVs vs SD-IIVs

Paper / Year	Season(s)	Design	Comparison	N	Outcome definition	rVE (95% CI)
Cocchio 2020	2011-12—2016-17	Retrospective cohort	aIIV3 vs SD-IIV	479,397	ICD selected P&I codes	**33 (25, 41)**
Izurieta 2019	2017-18	Retrospective cohort	aIIV3 vs SD-IIV3*	2,411,681	ICD influenza codes	**4.7 (0.9, 8.3)**
Izurieta 2019	2017-18	Retrospective cohort	aIIV3 vs SD-IIV4*	3,289,780	ICD influenza codes	2.5 (-0.8, 5.8)
Izurieta 2020	2018-19	Retrospective cohort	aIIV3 vs SD-IIV4*	2,645,932	ICD influenza codes	**6.5 (1.5, 11.3)**
Izurieta 2021	2019-20	Retrospective cohort	aIIV3 vs SD-IIV4*	4,149,964	ICD influenza codes	**6.8 (1.4, 11.9)**
Mannino 2012	2006-07—2008-09	Retrospective cohort	aIIV3 vs SD-IIV3	107,988	ICD P&I codes	**25 (2, 43)**
Robison 2018	2016-17	Retrospective cohort	aIIV3 vs SD-IIV	47,424	PCR-confirmed	**30.7 (8,48)**

RIVs vs SD-IIVs

Paper / Year	Season(s)	Design	Comparison	N	Outcome definition	rVE (95% CI)
Izurieta 2020	2019-20	Retrospective cohort	RIV3 vs SD-IIV4*	2,192,884	ICD influenza codes	**16.8 (9, 23.8)**

*Comparison is vs egg-based SD-IIV

P&I=pneumonia and influenza

Hospitalizations —Observational Studies

HD-IIVs vs aIIVs

Paper / Year	Season(s)	Design	Comparison	N	Outcome definition	rVE (95% CI)
Izurieta 2019a	2017-18	Retrospective cohort	HD-IIV3 vs aIIV3	9,955,054	ICD influenza codes	**7.7 (5.1, 10.2)**
Izurieta 2020	2018-19	Retrospective cohort	HD-IIV3 vs aIIV3	10,005,844	ICD influenza codes	-1.4 (-5.4, 2.4)
Izurieta 2021	2019-20	Retrospective cohort	HD-IIV3 vs aIIV3	9,738,946	ICD influenza codes	0.1 (-4.1, 4.2)
Van Aalst 2020	2016-17—2017-18	Retrospective cohort	HD-IIV3 vs aIIV3	2,124,713	ICD respiratory codes	**12 (3.3, 20)**

HD-IIVs vs RIVs

Paper / Year	Season(s)	Design	Comparison	N	Outcome definition	rVE (95% CI)
Izurieta 2020	2019-20	Retrospective cohort	HD-IIV3 vs RIV4	7,781,866	ICD influenza codes	**-11.8 (-21.1, -3.2)**

aIIVs vs RIVs

Paper / Year	Season(s)	Design	Comparison	N	Outcome definition	rVE (95% CI)
Izurieta 2020	2019-20	Retrospective cohort	aIIV3 vs RIV4	2,173,946	ICD influenza codes	**-12 (-21.8, -2.8)**

Description of Observational Studies: Summary

- Compared with randomized studies,
  - More influenza seasons represented;
  - More studies which address serious influenza illness outcomes (hospitalizations).
- Limitations
  - Data quality/risk of bias.
  - Majority of studies use diagnostic code-based outcome definitions (indirect evidence).
  - These limitations can be characterized through risk of bias assessment and GRADE.

Limitations

- Relatively fewer studies of RIV (particularly among the observational studies).
- Few to no data for some outcomes of interest for some vaccina comparisons
  - E.g., no data for influenza-related deaths for either aIIV or RIV.
- Most data from studies of HD-IIV and aIIV is for the trivalent versions of these vaccines, which are no longer in use, been replaced with quadrivalent formulations
- Potential for missing studies/papers.

Next Steps

- Addition of any further data.
- Discussion of GRADE (to include randomized and observational studies) and Evidence to Recommendations Framework at February ACIP meeting.

Thank you!