



## Influenza Vaccines for Persons Aged $\geq 65$ Years: Evidence to Recommendations (EtR) Framework

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Advisory Committee on Immunization Practices

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# Overview

- Background
- Evidence to Recommendations framework
- Work Group conclusions and proposed recommendation



# Background



## Influenza and Older Adults (Aged $\geq 65$ Years)

Season	Overall VE, % (all ages, viruses, and vaccine types)	$\geq 65$ yrs (all viruses and vaccine types)
2019-20	39 (32, 44)	39 (9, 59)
2018-19	29 (21, 35)	12 (-31, 40)
2017-18	38 (31, 43)	17 (-14, 39)
2016-17	40 (32, 46)	20 (-11, 43)
2015-16	48 (41, 55)	42 (6, 64)
2014-15	19 (10, 27)	32 (3, 52)
2013-14	52 (44, 59)	50 (16, 71)
2012-13	49 (43, 55)	26 (-10, 50)
2011-12	47 (36, 56)	43 (-18, 72)

- Persons aged  $\geq 65$  years are at increased risk of severe illness, hospitalization, and death due to influenza.
- Target population for annual influenza vaccination since the early 1960s.
- Influenza vaccines are often less effective compared with younger populations.

CDC, U.S. Flu VE Network,

<https://www.cdc.gov/flu/vaccines-work/past-seasons-estimates.html>

## Influenza Vaccines for Persons Aged $\geq 65$ Years

- All influenza vaccines currently available in the US, with the exception of the live attenuated influenza vaccine, are approved for ages  $\geq 65$  years.
  - Five standard-dose, unadjuvanted inactivated influenza vaccines (SD-IIVs).
  - One high-dose inactivated influenza vaccine (HD-IIV).
  - One adjuvanted inactivated influenza vaccine (aIIV).
  - One recombinant influenza vaccine (RIV).
- ACIP has previously expressed no preferential recommendation for any specific vaccine(s) for this age group.

## Fluzone High-Dose Quadrivalent (HD-IIV4)

- Approved as a trivalent (HD-IIV3) in 2009 for ages  $\geq 65$  years.
  - Four times the hemagglutinin (HA) dose/virus compared with SD-IIVs (60  $\mu\text{g}$  vs. 15  $\mu\text{g}$ ).
- Initial approval under accelerated pathway based upon demonstration of superior immunogenicity to SD-IIV3.
- Approval under traditional pathway in 2014 following demonstration of superior efficacy to standard-dose vaccine (SD-IIV3).
  - Two-season randomized trial among  $\sim 32,000$  participants ages  $\geq 65$  years.
- HD-IIV4 was approved in 2019 on the basis of noninferior immunogenicity to HD-IIV3, and replaced HD-IIV3 for the 2020-21 season.

## Fluad Quadrivalent (aIIV4)


- Approved in US as a trivalent (aIIV3) in 2015 for ages  $\geq 65$  years
  - In use in Europe as early as 1997.
  - Contains the adjuvant MF59
- Initially approved under the accelerated pathway based upon noninferior immunogenicity to unadjuvanted SD-IIV3.
- Quadrivalent (aIIV4) was compared with Tdap in two-season randomized trial among  $\sim 6,700$  persons ages  $\geq 65$  years.
  - Primary efficacy endpoint--prevention of PCR-confirmed protocol-defined influenza like illness (ILI) due to any influenza--not met (88% of antigenically characterized viruses from cases in aIIV4 arm were antigenically mismatched).
  - Efficacy was noted against PCR-confirmed CDC- and WHO-defined ILI due to any virus.
  - aIIV4 replaced aIIV3 for the 2021-22 season

## Flublok Quadrivalent (RIV4)

- Approved as a trivalent (RIV3) in 2013 for ages 18 through 49 years
  - Three times the HA dose/virus compared with SD-IIVs (45 µg vs. 15 µg).
  - Recombinant HA (no viruses or eggs used in production).
- Initially approved under the traditional pathway based upon efficacy demonstrated in a randomized placebo-controlled study among persons aged 18 through 49 years.
- Approved for ≥50 years in 2014 under accelerated pathway on the basis of immunogenicity studies among persons aged 50 and older.
- RIV4 demonstrated efficacy relative to SD-IIV4 in a single-season randomized study conducted among ~8600 persons ages ≥50 years.
  - RIV3 and RIV4 gained traditional approved for ages ≥50 years in 2017.
  - RIV4 replaced RIV3 for the 2018-19 season.



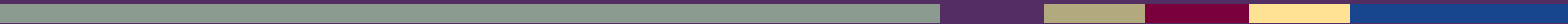
# Higher dose and Adjuvanted Influenza Vaccines Among Older Adults: Systematic Review, GRADE, and EtR

- Systematic review and GRADE summarized in detail previously
  - Question:
    - Do 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  $\geq 65$  years of age?
  - Relevant comparisons:
    - HD-IIV vs. SD-IIV
    - aIIV vs. SD-IIV
    - RIV vs. SD-IIV
    - HD-IIV vs. aIIV
    - HD-IIV vs. RIV
    - aIIV vs. RIV
  - *Higher dose and Adjuvanted Influenza Vaccines* replaces the collective term previously used for HD-IIV, aIIV, and RIV, Enhanced Influenza Vaccines (EIVs)
    - No standard definition of EIVs
- 

# PICO

<b>Population</b>	Persons aged $\geq 65$ years
<b>Intervention(s)</b>	Higher dose or adjuvanted influenza vaccines: HD-IIV aIIV RIV
<b>Comparators</b>	Standard-dose unadjuvanted inactivated influenza vaccines (SD-IIVs) Higher dose or adjuvanted influenza vaccines (vs one another)
<b>Critical Outcomes</b>	<p>Influenza illness            Influenza-associated outpatient/ER visits            Influenza-associated hospitalizations            Influenza-associated deaths            Any solicited systemic adverse event Grade <math>\geq 3</math>            Guillain-Barre syndrome</p> <p>} (due to any influenza viral type or subtype; lab confirmed, code-based, or clinical definitions)</p>
<b>Important Outcomes</b>	<p>Any solicited injection-site adverse event Grade <math>\geq 3</math>            Any Serious Adverse Event (SAE)</p>

# EtR Domain: Public Health Importance



## Estimated Burden of Influenza illnesses in the U.S., 2010-11 through 2015-16

- Rolfes et al (2017): estimated burden of influenza using data from routine influenza surveillance, outbreak investigations, and survey data describing proportions of persons seeking health care.
- Estimated annual burden (ranges):

Age group (years)	Outpatient visits	Hospitalizations	Excess Deaths	
			Pneumonia and Influenza	Respiratory and circulatory
<5	600,000—2,500,000	6,000—26,000	60—300	100—700
5-17	1,000,000—3,600,000	5,000—19,000	50—300	100—600
18-49	1,200,000—4,700,000	19,000—71,000	300—2,100	900—3,600
50-64	800,000—3,800,000	20,000—93,000	600—3,400	1,800—7,500
≥65	500,000—3,300,000	87,000—523,000	3,000—17,000	9,000—43,000

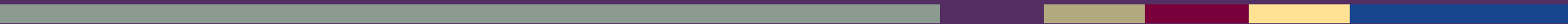
Rolfes et al. Annual estimates of the burden of seasonal influenza in the United States. *Influenza Other Respi Viruses* 2018;12:1232-137.

## WG Judgement: Public Health Importance

**Is the burden of influenza among persons aged  $\geq 65$  years a problem of public health importance?**

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

# EtR Domain: Benefits and Harms



# Relative Benefits and Harms of Higher dose and Adjuvanted vaccines

- GRADE summarized in February 2022.
- For this discussion, will focus on critical outcomes:
  - Benefits:
    - Influenza illness
    - Influenza associated outpatient and emergency department visits
    - Influenza associated hospitalizations
    - Influenza associated deaths.
  - Harms:
    - Any solicited systemic adverse event severity grade  $\geq 3$
    - Guillain-Barré syndrome



# Higher dose and Adjuvanted Vaccines vs. One Another: Benefits

Outcome	N of studies	Seasons	Certainty	Effect estimate	Vaccine favored
<b>HD-IIV vs. aIIV</b>					
Influenza illness	1 randomized	1	Level 4 (Very low)	RR 0.34 (0.04, 3,13)	-
Influenza outpatient/ER	3 retro cohort	2	Level 4 (Very low)	Rate ratio 1.06 (0.92, 1.23)	-
Influenza hospitalization	4 retro cohort	4	Level 4 (Very low)	Rate ratio 0.96 (0.90, 1.01)	-
<b>HD-IIV vs. RIV</b>					
Influenza illness	1 randomized	1	Level 4 (Very low)	0.26 (0.03, 1.18)	-
Influenza hospitalization	1 retro cohort	1	Level 2 (Low)	1.12 (1.03, 1.21)	Favors RIV
<b>aIIV vs. RIV</b>					
Influenza illness	1 randomized	1	Level 4 (Very low)	0.75 (0.18, 3.07)	-
Influenza hospitalization	1 retro cohort	1	Level 2 (Low)	1.12 (1.03, 1.22)	Favors RIV



## Higher dose and Adjuvanted Vaccines vs. One Another: Benefits—WG Considerations

- Among studies comparing higher dose and adjuvanted vaccines with one another, evidence is insufficient to inform a recommendation of any one over the others.
- Among studies providing safety data for these comparisons, no results favoring any vaccine for the selected critical outcomes.
  - Overall certainty Low, primarily due to imprecision stemming from low events counts and often small sample sizes



## Higher dose and Adjuvanted Vaccines vs. SD-IIVs: Benefits—HD-IIV vs SD-IIV

Outcome	N of studies	Seasons	Certainty	Effect estimate	Vaccine favored
<b>HD-IIV vs. SD-IIV</b>					
Influenza illness	1 randomized	2	Level 1 (High)	RR: 0.76 (0.64, 0.90)	Favors HD-IIV
Influenza outpatient/ER	4 retro cohort	4	Level 3 (Low)	Rate ratio 0.87 (0.76, 0.99)	Favors HD-IIV
	1 case-control	4	Level 3 (Very Low)	OR: 0.91 (0.73, 1.12)	-
Influenza hospitalization	1 cluster randomized	1	Level 2 (Moderate)	Rate ratio 0.79 (0.66, 0.96)	Favors HD-IIV
	2 randomized	5	Level 2 (Moderate)	RR 1.00 (0.47, 2.12)	-
	8 retro cohort	9	Level 3 (Low)	Rate ratio 0.92 (0.90, 0.94)	Favors HD-IIV
	2 observational	1	Level 3 (Low)	OR: 0.71 (0.57, 0.88)	Favors HD-IIV
Influenza death	2 retro cohort	3	Level 3 (Low)	Rate ratio 0.67 (0.56, 0.81)	Favors HD-IIV

## Higher dose and Adjuvanted Vaccines vs. SD-IIVs: Benefits—aIIV vs SD-IIV

Outcome	N of studies	Seasons	Certainty	Effect estimate	Vaccine favored
<b>aIIV vs. SD-IIV</b>					
Influenza illness	1 randomized	1	Level 2 (Moderate)	RR 1.03 (0.89, 1.19)	-
Influenza outpatient/ER	2 retro cohort	1	Level 4 (Very low)	Rate ratio 1.00 (0.97 to 1.03)	-
	2 observational	2	Level 3 (Low)	OR 0.64 (0.52, 0.79)	Favors aIIV
Influenza hospitalization	1 cluster randomized	1	Level 2 (Moderate)	Rate ratio 0.79 (0.65, 0.96)	Favors aIIV
	3 retro cohort	3	Level 2 (Low)	Rate ratio 0.95 (0.92, 0.98)	Favors aIIV
	2 observational	4	Level 3 (Low)	RR 0.75 (0.58 to 0.97)	Favors aIIV


## Higher dose and Adjuvanted Vaccines vs. SD-IIVs: Benefits—RIV vs SD-IIV

Outcome	N of studies	Seasons	Certainty	Effect estimate	Vaccine favored
<b>RIV vs. SD-IIV</b>					
Influenza illness	2 randomized	2	Level 2 (Moderate)	RR 0.82 (0.57, 1.17)	-
Influenza hospitalization	1 retro cohort	1	Level 3 (Low)	Rate ratio 0.83 (0.76, 0.91)	Favors RIV

## Higher dose and Adjuvanted Vaccines vs. SD-IIVs: Harms

Outcome	N of studies	Certainty	Effect estimate	Vaccine favored
<b>HD-IIV vs. SD-IIV</b>				
Systemic AE grade $\geq 3$	2 randomized	Level 3 (Low)	Risk Ratio 0.95 (0.20, 4.53)	-
Guillain-Barré Syndrome	1 randomized	Level 3 (Low)	Not estimable	-
<b>aIIV vs. SD-IIV</b>				
Systemic AE grade $\geq 3$	4 randomized	Level 3 (Low)	Risk Ratio 0.77 (0.34, 1.76)	-
Guillain-Barré Syndrome	1 randomized	Level 3 (Low)	Risk Ratio 0.33 (0.01, 8.16)	-
<b>RIV vs. SD-IIV</b>				
Systemic AE grade $\geq 3$	2 randomized	Level 3 (Low)	Risk Ratio 0.28 (0.05, 1.67)	-
Guillain-Barré Syndrome	1 retro cohort	Level 4 (Very Low)	Not estimable	-

## WG Considerations--Benefits

- Among the three vaccines, the most data are available to support HD-IIV.
    - Evidence favoring its use for all benefit outcomes.
    - Includes evidence of benefit from a large randomized trial (High certainty)
  - Among outcomes, the most data are available for influenza hospitalizations—a relatively common and severe outcome for this age group.
    - Evidence favoring each of the vaccines vs. SD-IIV, though depth of data varies: Most for HD-IIV (Moderate certainty), less for allIV (Moderate certainty), least for RIV (Low certainty).
  - Relative VE varies with season:
    - Benefits of one vaccine compared to another are not static,
    - Relative benefit might not be observed in every season.
    - What performs best in one season might not in another.
- 

## WG Considerations--Safety

- Certainty ratings low or very low for safety outcomes.
  - This is mainly due to downgrading for imprecision.
    - Low event counts/small sample sizes in some studies.
    - Guillain-Barré is a rare outcome.
- Not a reflection of lack of safety
  - Each has demonstrated safety in prelicensure trials
  - Increased frequency of some reactogenicity events in some studies of HD-IIV and allIV compared with Sd-IIV, but most events mild or moderate in severity.

## Benefits and Harms

What is the overall certainty of the evidence for the critical outcomes?

HD-IIV3 vs SD-IIV	aIIV3 vs SD-IIV	RIV vs SD-IIV
<b>Effectiveness:</b> <ul style="list-style-type: none"><li>○ No studies found</li><li>○ 4 (very low)</li><li>○ 3 (low)</li><li>○ 2 (moderate)</li><li>○ 1 (high)</li></ul>	<b>Effectiveness:</b> <ul style="list-style-type: none"><li>○ No studies found</li><li>○ 4 (very low)</li><li>○ 3 (low)</li><li>○ 2 (moderate)</li><li>○ 1 (high)</li></ul>	<b>Effectiveness:</b> <ul style="list-style-type: none"><li>○ No studies found</li><li>○ 4 (very low)</li><li>○ 3 (low)</li><li>○ 2 (moderate)</li><li>○ 1 (high)</li></ul>
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## WG Judgement: Benefits and Harms

How substantial are the desirable anticipated effects?

- Minimal
- Small
- Moderate
- Large
- Varies
- Don't know

## WG Judgement: Benefits and Harms

How substantial are the undesirable anticipated effects?

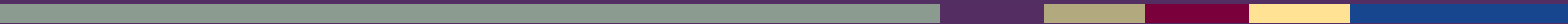
- Minimal
- Small
- Moderate
- Large
- Varies
- Don't know

## WG Judgement: Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

- Favors intervention
- Favors comparison
- Favors both
- Favors neither
- Varies
- Don't know

# EtR Domain: Values



## Values—WG Discussion

- No literature found reflecting values of U.S. seniors concerning higher dose and adjuvanted vaccines specifically, or the relative importance of the selected outcomes.
- Recent CMS data analyses suggest majority of community-dwelling Medicare beneficiaries aged  $\geq 65$  years received these vaccines in recent seasons.
  - Suggests that some recipients seek these vaccines;
  - However, provider choices and recommendations also likely a factor.

## WG Judgement: Values

Does the target population feel that the desirable effects are large relative to the undesirable effects?

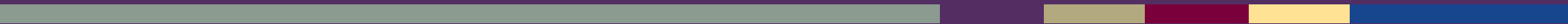
- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

## WG Judgement: Values

**Is there important uncertainty about or variability in how much people value the main outcomes?**

- Important uncertainty or variability
- Probably important uncertainty or variability
- Probably not important uncertainty or variability**
- Not important uncertainty or variability
- No known undesirable outcomes

# EtR Domain: Acceptability





## Uptake of HD-IIV, aIIV, and RIV Among Medicare Beneficiaries

- Analyses of vaccine effectiveness among Medicare beneficiaries suggest most aged  $\geq 65$  years received a higher dose or adjuvanted vaccine in recent seasons
  - Vaccines received by Medicare beneficiaries aged  $\geq 65$  (Izurieta et al analytic sets, (n=12-13 million each season):

Season	HD-IIV3	aIIV3	RIV4	Total
2017-18 <sup>2</sup>	63%	11%	-	74%
2018-19 <sup>3</sup>	62%	16%	2%	80%
2019-20 <sup>4</sup>	56%	20%	5%	81%

1. Izurieta HS, et al. Relative Effectiveness of Cell-Cultured and Egg-Based Influenza Vaccines Among Elderly Persons in the United States, 2017-2018. J Infect Dis. 2019 Sep 13;220(8):1255-64.
2. Izurieta HS, et al. Relative Effectiveness of Influenza Vaccines Among the United States Elderly, 2018-2019. J Infect Dis. 2020 Jun 29;222(2):278-87.
3. Izurieta HS, et al. Comparative Effectiveness of Influenza Vaccines Among US Medicare Beneficiaries Ages 65 Years and Older During the 2019-2020 Season. Clin Infect Dis. 2021 Dec 6;73(11):e4251-e9.

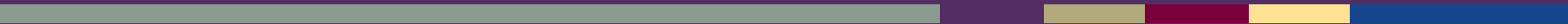
## WG Judgement: Acceptability

Is the intervention acceptable to key stakeholders?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

# EtR Domain: Resource Use

Use for section headers



# Economic Evaluation of Higher Dose and Adjuvanted Influenza Vaccines

- Multiple published economic evaluations of HD-IIV and aIIV compared with standard vaccines.
- Given the possibility of a recommendation for more than one higher dose or adjuvanted vaccine over SD-IIVs, an economic analysis was conducted.

*Colrat et al, Vaccine 2021;39:A42-A50*

*Loperto et al Hum Vacc Immunother 2019;15:1035-1047*

# **Economic Analysis of Higher dose and Adjuvanted Influenza Vaccines for Adults Aged $\geq 65$ Years**

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Immunization Services Division  
NCIRD, CDC



## Objective

- To conduct a cost effectiveness analyses of use of higher dose and adjuvanted influenza vaccines (HD-IIV, RIV, and aIIV) for adults aged 65 and over in the US, compared with standard-dose (SD-IIV) influenza vaccines, from the societal perspective.



## Base Case

- Average of 2017/18- 2019/20 influenza seasons (disease burden, vaccination coverage, efficacy/effectiveness).

### Base Case Incremental CE Ratio (\$/QALY)

HD vs SD-IIV	aIIV vs SD-IIV	RIV vs SD-IIV
52,600	60,100	cs

### Base Case Average CE Ratio (\$/QALY)

HD vs No vaccine	aIIV vs No vaccine	RIV vs No vaccine	SD-IIV vs No vaccine
6,600	7,600	cs	cs

## Estimated Number of Influenza Cases, Hospitalizations, and Deaths: Base Case

	# Cases	# Medically Attended Cases	# Hospitalizations	# Deaths	QALY Lost
<b>No Vaccination</b>	4,876,000	2,731,000	443,000	39,100	430,000
<b>SD-IIV</b>	4,362,000	2,443,000	397,000	34,900	385,000
<b>HD-IIV</b>	4,200,000 -162,000	2,352,000 -91,000	382,000 -15,000	33,600 -1,300	371,000 -14,000
<b>aIIV</b>	4,211,000 -151,000	2,358,000 -85,000	383,000 -14,000	33,700 -1,200	372,000 -13,000
<b>RIV</b>	3,954,000 -408,000	2,214,000 -229,000	359,000 -38,000	31,700 -3,200	349,000 -36,000

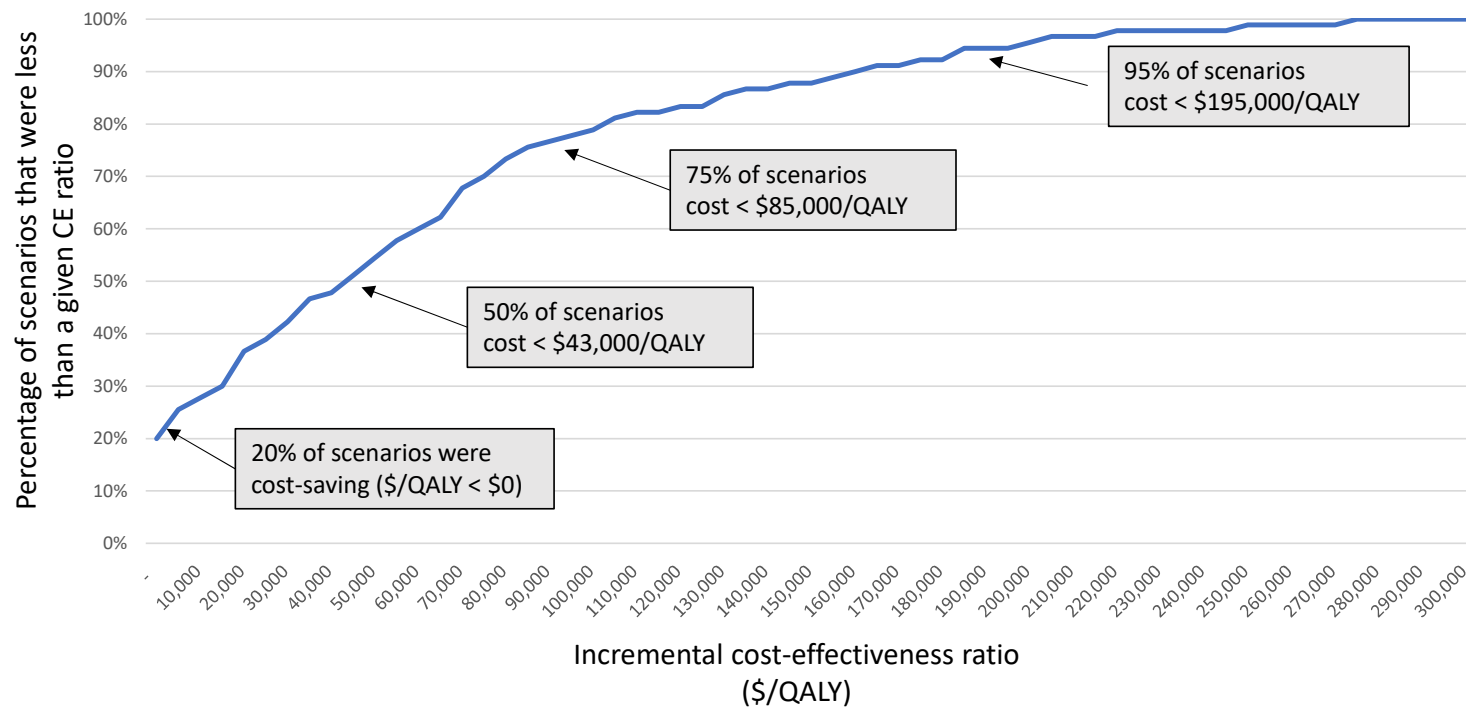


## Incremental CE ratio (\$/QALY):

2017-18, 2018-19 and 2019-20 vaccine effectiveness data applied to 10 consecutive influenza seasons

Season	2017/18 VE			2018/19 VE			2019/20 VE		
	HD vs SD-IIV	aIIV vs SD-IIV	RIV vs SD-IIV	HD vs SD-IIV	aIIV vs SD-IIV	RIV vs SD-IIV	HD vs SD-IIV	aIIV vs SD-IIV	RIV vs SD-IIV
2010/11	18,300	99,100	cs	65,700	26,000	cs	68,400	50,500	13,700
2011/12	90,200	271,200	45,400	196,400	107,500	1,700	202,400	162,300	79,900
2012/13	4,600	79,900	cs	48,800	11,800	cs	51,200	34,600	300
2013/14	20,100	100,600	200	67,300	27,800	cs	70,000	52,100	15,600
2014/15	1,800	69,600	cs	41,500	8,300	cs	43,800	28,700	cs
2015/16	67,200	215,900	30,500	154,400	81,400	cs	159,300	126,400	58,800
2016/17	21,400	116,700	cs	77,300	30,500	cs	80,400	59,300	16,000
2017/18	cs	37,600	cs	16,900	cs	cs	18,500	7,400	cs
2018/19	48,400	181,300	15,500	126,400	61,100	cs	130,700	101,300	40,800
2019/20	73,100	246,500	30,300	174,800	89,700	cs	180,500	142,100	63,300

# Incremental Cost-effectiveness Curve



## Summary

- Incremental CE ratios for higher dose and adjuvanted vaccines vs SD-IIVs vary considerably based upon underlying VE and influenza season severity.
- In modeling various assumptions
  - 20% of scenarios were cost-saving
  - 95% scenarios were under \$195,000/QALY



## Limitations

- Modeling work indicates substantial uncertainty in estimates of value due to multiple product comparisons and in variability of influenza burden and VE from season to season.
- VE assumptions were derived from estimates obtained in retrospective cohort study of vaccines for prevention of influenza-associated hospitalizations.
  - Not from randomized study data
  - VE might differ for different outcomes (e.g., illnesses, outpatient visits, deaths).



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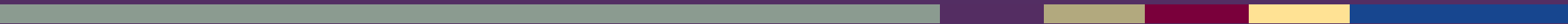


## WG Judgement: Resource Use

Is the intervention a reasonable and efficient allocation of resources?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

# EtR Domain: Equity



## Disparities in Influenza Vaccination Persons Aged $\geq 65$ Years

- Racial and ethnic disparities in overall influenza vaccine coverage and rates of severe influenza illness have been documented.
- Mahmud et al (2021)
  - Receipt of HD-IIV3 vs all other seasonal influenza vaccines as a group, Medicare beneficiaries aged  $\geq 65$  years during 2015-16 influenza season
    - Of 12.6M vaccinated, 6.6M (52.7%) received HD-IIV3 and 5.9M (47.3%) received another vaccine
    - ORs for HD-IIV receipt adjusted for geographic region, income, chronic conditions, health-care use):

Group	Adjusted OR for receipt of HD-IIV vs SD-IIV	95% CI
White	reference	reference
Black	0.68	(0.68, 0.69)
Asian	0.71	(0.71, 0.72)
Hispanic	0.74	(0.73, 0.74)



## Equity—WG Discussion

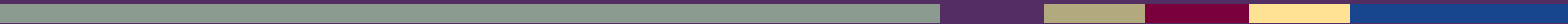
- Potential impact depends upon underlying causes.
- Potential factors include (but are not limited to) cost, differences in practice settings, differences in linkage to health care
- Noted that the Mahmud study occurred during 2015-16.
  - aIV not yet introduced; RIV still relatively new to market.
- While not possible to know whether a recommendation for higher dose or adjuvanted vaccines would positively impact equity, there is not a basis to predict negative impact.

## WG Judgement: Equity

### What would be the impact on health equity?

- Reduced
- Probably reduced
- Probably no impact
- Probably increased
- Increased
- Varies
- Don't know

# EtR Domain: Feasibility



## WG Considerations: Feasibility

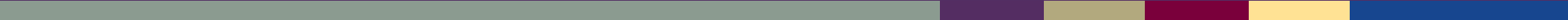
- Analyses of CMS data suggest most community dwelling CMS beneficiaries aged 65 and older have already received a higher dose or adjuvanted influenza vaccine during recent seasons (2017-18 through 2019-20).
- CMS reimburses for all influenza vaccines for this age group.
  - HD-IIV, RIV, and aIIV are reimbursed at a higher rate than SD-IIVs (as of 2021-22, ~\$65.00-66.00 vs ~20.00-28.00 for single-dose presentations of SD-IIVs).
- Higher dose and adjuvanted influenza vaccines are similar in administration and storage to other intramuscular influenza vaccines.

## WG Judgement: Feasibility

Is the intervention feasible to implement?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

# EtR Summary



## EtR WG Judgement Summary

Domain	Considerations <i>Intervention = higher dose or adjuvanted vaccines over SD-IIVs (comparators) for persons aged ≥65 years</i>	WG Judgment
<b>Public Health Importance</b>	Is influenza among persons aged ≥65 years a problem of public health importance?	Yes
<b>Benefits and Harms</b>	<p>Overall certainty of the evidence for the critical outcomes (vs SD-IIVs):</p> <p style="text-align: right;">Efficacy/effectiveness Safety</p> <p>How substantial are the desirable anticipated effects? How substantial are the potential undesirable effects? Do the desirable effects outweigh the undesirable effects?</p>	<p>Low Low (HD-IIV, aIIV) Very Low (RIV) Moderate / Varies Minimal Favors intervention</p>
<b>Values</b>	<p>Does the target population feel that the desirable effects are large relative to the undesirable effects? Is there important uncertainty about or variability in how much people value the main outcomes?</p>	<p>Probably yes  Probably not important uncertainty or variability</p>
<b>Acceptability</b>	Is the intervention acceptable to key stakeholders?	Yes
<b>Resource use</b>	Is the intervention a reasonable and efficient use of resources?	Yes
<b>Equity</b>	What would be the impact on health equity?	Probably increased
<b>Feasibility</b>	Is the intervention feasible to implement?	Yes

# Balance of Consequences

Undesirable  
consequences  
*clearly outweigh*  
desirable  
consequences in  
most settings

Undesirable  
consequences  
*probably outweigh*  
desirable  
consequences in  
most settings

The balance  
between desirable  
and undesirable  
consequences is  
*closely balanced or*  
*uncertain*

Desirable  
consequences  
*probably outweigh*  
undesirable  
consequences in  
most settings

Desirable  
consequences  
*clearly outweigh*  
undesirable  
consequences in  
most settings

There is  
insufficient  
evidence to  
determine the  
balance of  
consequences



**Is there sufficient evidence to move forward with a recommendation?**

Yes

No

## Potential Recommendations

No change in recommendations:

Any age-appropriate vaccine is recommended for persons aged  $\geq 65$  years

HD-IIV4 is recommended, when available, over other influenza vaccines for persons aged  $\geq 65$  years.

If HD-IIV4 is not readily available, any age-appropriate vaccine may be used


HD-IIV4 is recommended, when available, over other influenza vaccines for persons aged  $\geq 65$  years.

If HD-IIV4 is not readily available, aIIV4 or RIV4 is recommended.


If none of these three vaccines is available, any age-appropriate vaccine may be used

HD-IIV4, aIIV4, or RIV4 are recommended, when available, over other influenza vaccines for persons aged  $\geq 65$  years. If none of these three vaccines is available, any age-appropriate vaccine may be used


## Potential Recommendations—WG Considerations

- Randomized trials, ideally against lab-confirmed outcomes, are the most desirable evidence.
    - Not easily executed over multiple seasons.
    - Influenza vaccine effectiveness is variable; difficult to generalize findings from one or a few seasons.
    - Only two randomized efficacy trials comparing influenza vaccines against lab confirmed outcomes—one for HD-IIV vs SD-IIV, the other for RIV vs SD-IIV, covering 2 and 1 season, respectively.
  - While randomized trials are crucial, decisions regarding potential preferential recommendations might need also to draw from observational studies.
  - A recommendation to use any one of the three higher dose or adjuvanted vaccines provides balance of science and practicality, given variability of influenza seasons and vaccine effectiveness.
- 

## Potential Recommendations—WG Considerations

- While randomized trials are critical, decisions regarding potential preferential recommendations for influenza vaccines might need also to draw from observational studies.
  - It was acknowledged that the most data, for the most outcomes, are available to support the high dose vaccine,
    - Randomized trial of RIV4 did not demonstrate benefit for primary outcome for 65 and older, but did for other outcomes in this subgroup and for those 50 and older.
    - Evidence to support adjuvanted vaccine from one cluster randomized and multiple observational studies.
  - A recommendation for a single vaccine over all others might lead to confusion if it does not demonstrate consistent benefit over future seasons.
  - A recommendation for any of the three higher dose or adjuvanted vaccines provides balance of science and practicality, given variability of influenza seasons and vaccine effectiveness.
- 

## Potential Recommendations—WG Considerations

- Finally, as noted earlier, there are fewer data comparing HD-IIV, aIIV, and RIV with one another.
  - Most data for HD-IIV vs aIIV:
    - Some observational studies show greater benefit for one or other, but no differences in pooled analyses;
    - No differences in safety outcomes of interest in one randomized study.
  - Some suggestion of greater benefit of RIV relative to both HD-IIV and aIIV,
    - But these data are from one observational study including one season.
  - Current evidence insufficient to recommend one vaccine over the others .
  - However, it is likely that we will have more comparative data to examine in the near term (possibly with current quadrivalent formulations).
- 

## Potential Recommendations—WG Considerations

- Other points spoke to acceptability and feasibility:
  - A recommendation for one of three vaccines when available provides flexibility for providers--for example, for those who care for adults across an age spectrum, RIV (which is approved for ages 18 years and older) might be more practical than HD-IIV or aIIV.
  - This approach minimizes the risks associated with a recommendation for one vaccine over all others if there are unexpected delays in vaccine availability or manufacturing problems.



For more information, contact CDC  
1-800-CDC-INFO (232-4636)  
TTY: 1-888-232-6348 [www.cdc.gov](http://www.cdc.gov)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

