



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

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# Overview

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



# Background



## Influenza and Older Adults (Aged ≥65 Years)

Season	Overall VE, % (all ages, viruses, and vaccine types)	≥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 ≥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.



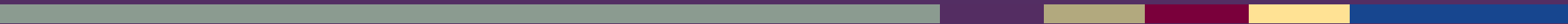
# Higher dose and Adjuvanted Influenza Vaccines Among Older Adults: Systematic Review, GRADE, and EtR

- 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>	Any solicited injection-site adverse event Grade $\geq 3$ Any Serious Adverse Event (SAE)

# 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

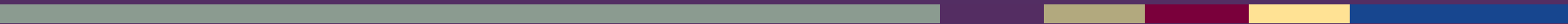
Rolfes et al. Annual estimates of the burden of seasonal influenza in the United States. *Influenza Other Respi Viruses* 2018;12:1232-137.

## 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 allIIV (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?

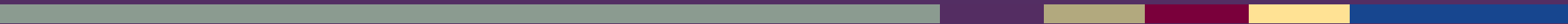
- Minimal
- Small
- Moderate
- Large
- Varies
- Don't know

## 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?

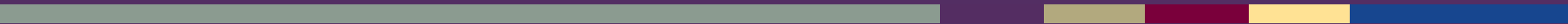
- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

## 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>1</sup>	63%	11%	-	74%
2018-19 <sup>2</sup>	62%	16%	2%	80%
2019-20 <sup>3</sup>	56%	20%	5%	81%

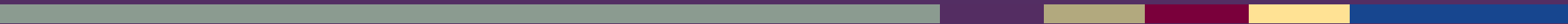
1. Izurieta HS, et al. Relative Effectiveness of Cell-Cultured and Egg-Based Influenza Vaccines Among Elderly Persons in the United States, 2017-2018. J Infect Dis. 2019 Sep 13;220(8):1255-64.
2. Izurieta HS, et al. Relative Effectiveness of Influenza Vaccines Among the United States Elderly, 2018-2019. 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



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

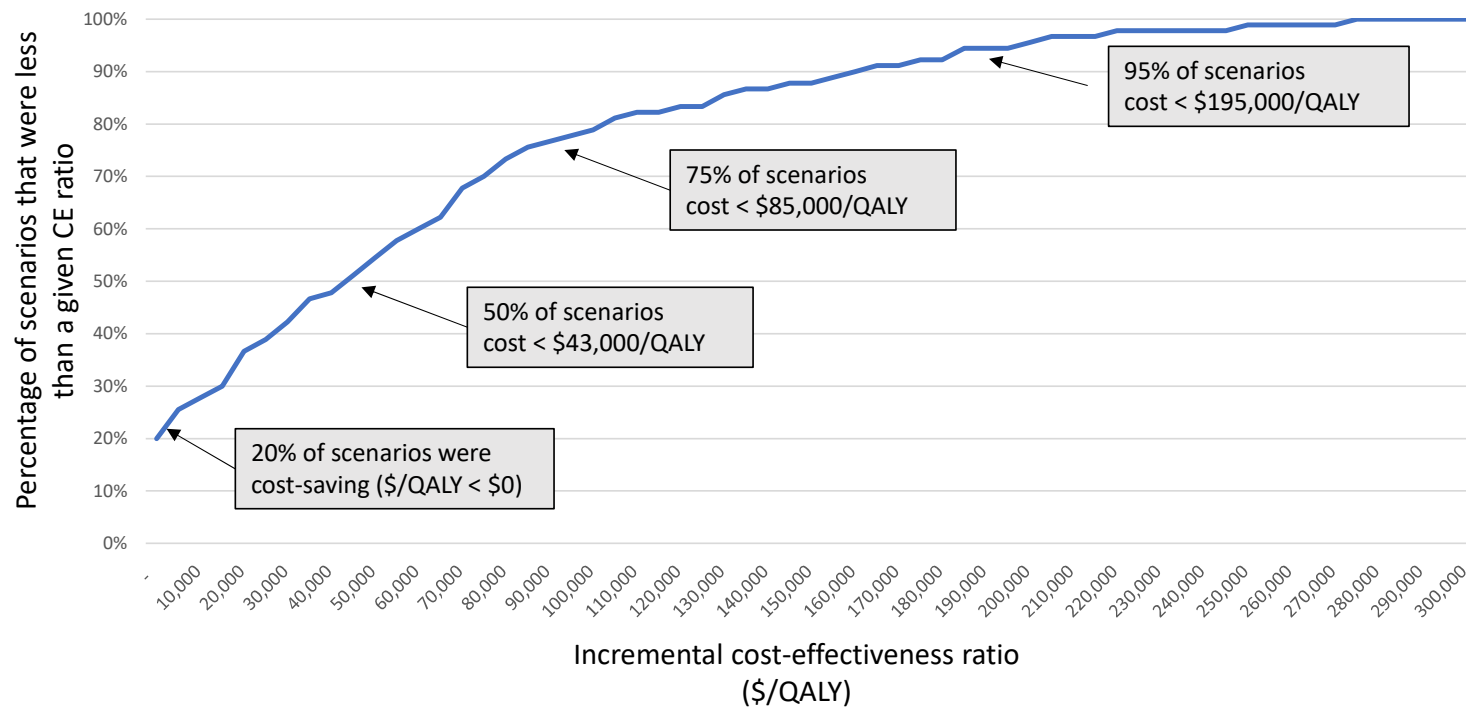


## Incremental CE ratio (\$/QALY):

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

-	2017/18 VE			2018/19 VE			2019/20 VE		
Season	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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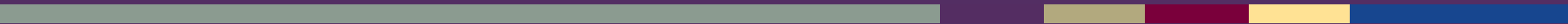


## WG Judgement: Resource Use

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

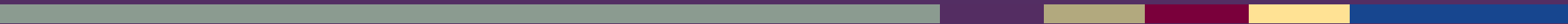
- Potential impact depends upon underlying causes.
- Potential factors include (but are not limited to) cost, differences in practice settings, differences in linkage to health care
- Noted that the Mahmud study occurred during 2015-16.
  - allV not yet introduced; RIV still relatively new to market.
- 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

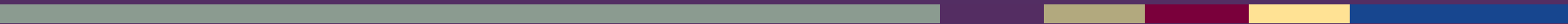
- Analyses of CMS data suggest most community dwelling CMS beneficiaries aged 65 and older have already received a higher dose or adjuvanted influenza vaccine during recent seasons (2017-18 through 2019-20).
- CMS reimburses for all influenza vaccines for this age group.
  - HD-IIV, RIV, and aIIV are 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





# 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.
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## 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.

