



# Influenza Vaccines for Older Adults: GRADE Summary

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## Question

Do the relative benefits and harms of H5N1IV, aIV, and RIV (referred to collectively as enhanced influenza vaccines, or EIVs) as compared with one another and with standard-dose unadjuvanted influenza vaccines (SD-IIVs) favor the use of any one or more of these vaccines over other age-appropriate influenza vaccines for persons  $\geq 65$  years of age.

# PICO

- Population: Adults ages 65 years and older
- Interventions: EIVs: HDIV, aIV, RIV (quadrivalents and trivalent)
- Comparators: SD-IIV (quadrivalents and trivalent); EIVs
- Outcomes:
  - Benefits: Prevention of
    - Influenza illnesses Critical
    - Influenza-associated outpatient/ER visits Critical
    - Influenza-associated hospitalizations Critical
    - Influenza-associated deaths Critical
  - Harms: Occurrence of
    - Any Serious Adverse Event (SAE) Important
    - Any solicited injection site adverse reaction Grade  $\geq 3$  Important
    - Any solicited systemic adverse reaction Grade  $\geq 3$  Critical
    - Guillain-Barré Syndrome Critical

# Notes for the Slides Which Follow

- Six vaccine comparisons:

EIVs vs SDIVs	EIVs vs one another
HD-IIV vs SD-IIV	HD-IIV vs aIIV
aIIV vs SD-IIV	HD-IIV vs RIV
RIV vs SD-IIV	aIIV is RIV

- Analyses considered influenza seasons separately where possible.
- Comparisons of trivalent and quadrivalent vaccines are combined.
- In cases where separate estimates were made for different IIV comparator vaccines (SDIV3, SDIV4, eggbased, cellbased), these slides present data for comparisons to SDIV4 (eggbased if specified).
- Estimates for composite outcomes (e.g, combined inpatient/outpatient visits; hospitalizations/ER visits) are not included in main analyses/GRADE.

- **Comparison 1: HD-IIV vs SD-IIV**
- Comparison 2: aIIV vs SD-IIV
- Comparison 3: RIV vs SD-IIV
  
- Comparison 4: HD-IIV3 vs aIIV3
- Comparison 5: HD-IIV3 vs RIV4
- Comparison 6: aIIV3 vs RIV4

# HD-IIV3 vs SD-IIV: Benefits

Outcome	Studies, n Design	Seasons	Relative Risk† or Rate Ratio§ (95%CI)	Importance	Certainty
Influenza illnesses	1 RCT†	2	<b>0.71 (0.51, 0.99)</b>	Critical	Level 1 High
Influenza outpatient/ER visits*	4 retro cohort §	4	<b>0.87 (0.76, 0.99)</b>	Critical	Level 2 Moderate
Influenza hospitalizations	2 RCT† 1 cluster RC§ 8 retro cohort § 1 retro cohort † 1 case-control †	10	1.00 (0.47, 2.12) <b>0.79 (0.66, 0.95)</b> <b>0.92 (0.90, 0.94)</b> <b>0.71 (0.57, 0.88)</b>	Critical	Level 2 Moderate
Influenza deaths	2 retro cohort §	3	<b>0.67 (0.56, 0.81)</b>	Critical	Level 2 Moderate

RCT= randomized study; retro cohort=retrospective cohort

\* An additional casecontrol study addressing this outcome is omitted here in favor of the higher certainty evidence from the retrospective cohort studies.

† person denominator

§ person-time denominator

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# HD-IIV3 vs SD-IIV: Harms

Outcome	Studies, n Design	Relative Risk† or Rate Ratio§ (95%CI)	Importance	Certainty
Any SAE	7 RCT†	<b>0.91 (0.85, 0.97)</b>	Important	Level 1 High
Any solicited injection site AE Grade $\geq 3$	2 RCT†	4.91 (0.85, 28.36)	Important	Level 3 Low
Any solicited systemic AE Grade $\geq 3$	3 RCT†	0.95 (0.20, 4.53)	Critical	Level 3 Low
Guillain-Barré syndrome*	1 RCT†	Not estimable	Critical	Level 3 Low

RCT= randomized study

\* One RCT comparing HD-IIV3 (2606 persons) and IIV4 (2604 participants) included Guillain-Barré syndrome as an adverse event of special interest; no cases were reported in the paper

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- **Comparison 2: aIIV vs SD-IIV**
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- Comparison 5: HD-IIV3 vs RIV4
- Comparison 6: aIIV3 vs RIV4

# aIIV3 vs SD-IIV: Benefits

Outcome	Studies, n Design	Seasons	Relative Risk† or Rate Ratio§ (95%CI)	Importance	Certainty
Influenza illnesses	1 RCT†	1	1.03 (0.89, 1.19)	Critical	Level 2 Moderate
Influenza outpatient/ER visits	2 retro cohort§ 1 retro cohort† 1 case-control †	3	0.83 (0.50, 1.37) 0.60 (0.40, 0.91)	Critical	Level 2 Moderate
Influenza hospitalizations	1 cluster RC‡ 4 retro cohort§ 1 prospective cohort†	11	0.79 (0.65, 0.96) 0.88 (0.80, 0.97) 0.75 (0.57, 0.99)	Critical	Level 2 Moderate
Influenza deaths	No studies				

RCT= randomized study; retro cohort=retrospective cohort

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Influenza outpatient/ER visits	2 retro cohort* 1 retro cohort† <b>1 case-control †</b>	3	0.83 (0.50, 1.37) <b>0.60 (0.40, 0.91)</b>	Critical	Level 2 Moderate
Influenza hospitalizations	1 cluster RCT 4 retro cohort * 1 prospective cohort †	11	0.79 (0.65, 0.96) 0.88 (0.80, 0.97) 0.75 (0.57, 0.99)	Critical	Level 2 Moderate
Influenza deaths	No studies				

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# aIIV3 vs SD-IIV: Harms

Outcome	Studies, n Design	Relative Risk† or Rate Ratio§ (95%CI)	Importance	Certainty
Any SAE	8 RCT	1.07 (0.92, 1.26)	Important	Level 2 Moderate
Any solicited injection site AE Grade $\geq 3$	4 RCT	3.39 (1.32, 8.72)§	Important	Level 3 Low
Any solicited systemic AE Grade $\geq 3$	4 RCT	0.77 (0.34, 1.75)	Critical	Level 3 Low
Guillain-Barré syndrome	1 RCT * 1 retro cohort †	0.33 (0.01, 8.16) Not estimable	Critical	Level 3 Low

RCT= randomized study; retro cohort=retrospective cohort

\* One RCT reported one case of GBS in the SD-IIV3 arm.

† One retrospective cohort study reported 0 “definite”, “probable”, or “possible” cases in either arm during a 0-42 day window.

§ Driven by one study; paper specifies that there was no severe pain in either group

# aIIV3 vs SD-IIV: Harms

Outcome	Studies, n Design	Relative Risk† or Rate Ratio§ (95%CI)	Importance	Certainty
Any SAE	8 RCT	1.07 (0.92, 1.26)	Important	Level 2 Moderate
Any solicited injection site AE Grade $\geq 3$	4 RCT	<b>3.39 (1.32, 8.72)§</b>	Important	Level 3 Low
Any solicited systemic AE Grade $\geq 3$	4 RCT	0.77 (0.34, 1.75)	Critical	Level 3 Low
Guillain-Barré syndrome	1 RCT * 1 retro cohort †	0.33 (0.01, 8.16) Not estimable	Critical	Level 3 Low

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- Comparison 2: aIIV vs SD-IIV
- **Comparison 3: RIV vs SD-IIV**
  
- Comparison 4: HD-IIV3 vs aIIV3
- Comparison 5: HD-IIV3 vs RIV4
- Comparison 6: aIIV3 vs RIV4

# RIV vs SD-IIV: Benefits

Outcome	Studies, n Design	Seasons	Relative Risk†/Rate Ratio§	Importance	Certainty
Influenza illnesses	2 RCT†	2	0.82 (0.57, 1.1)§	Critical	Level 2 Moderate
Influenza outpatient/ER visits	No studies				
Influenza hospitalizations	1 retro cohort§	1	0.83 (0.76, 0.91)	Critical	Level 2 Moderate
Influenza deaths	No studies				

RCT= randomized study; retro cohort=retrospective cohort

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Influenza outpatient/ER visits	No studies				
Influenza hospitalizations	1 retro cohort§	1	<b>0.83 (0.76, 0.91)</b>	Critical	Level 2 Moderate
Influenza deaths	No studies				

RCT= randomized study; retro cohort=retrospective cohort

†person denominator

§person-time denominator

# RIV vs SD-IIV: Harms

Outcome	Studies, n Design	Relative Risk†/Rate Ratio§	Importance	Certainty
Any SAE	5 RCT *	1.03 (0.84, 1.26)	Important	Level 3 Low
Any solicited injection site AE Grade $\geq 3$	2 RCT	0.68 (0.27, 1.69)	Important	Level 3 Low
Any solicited systemic AE Grade $\geq 3$	2 RCT	0.28 (0.05, 1.71)	Critical	Level 3 Low
Guillain-Barré syndrome	1 retro cohort †	Not estimable	Critical	Level 4 Very low

RCT= randomized study; retro cohort=retrospective cohort

\*Largest 2 studies include persons ages  $\geq 50$  years.

†One cohort study examined Guillain-Barré syndrome among persons receiving RIV3 vs SD-IIV3 and reported a total of 4 cases, all among SD-IIV3 recipients, using a 41-day post vaccination window.

# RIV vs SD-IIV: Harms

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Any solicited injection site AE Grade $\geq 3$	2 RCT	0.68 (0.27, 1.69)	Important	Level 3 Low
Any solicited systemic AE Grade $\geq 3$	2 RCT	0.28 (0.05, 1.71)	Critical	Level 3 Low
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- Comparison 2: aIIV vs SD-IIV
- Comparison 3: RIV vs SD-IIV
  
- **Comparison 4: HD-IIV3 vs aIIV3**
- Comparison 5: HD-IIV3 vs RIV4
- Comparison 6: aIIV3 vs RIV4

# HD-IIV3 vs aIIV3: Benefits

Outcome	Studies, n Design	Seasons	Relative Risk†/Rate Ratio§	Importance	Certainty
Influenza illnesses	1 RCT†	1	0.34 (0.04, 3.13)	Critical	Level 4 Very low
Influenza outpatient/ER visits	3 retro cohort§	2	1.06 (0.92, 1.21)	Critical	Level 2 Low
Influenza hospitalizations	4 retro cohort§	4	0.96 (0.90, 1.01)	Critical	Level 3 Low
Influenza deaths	No studies				

RCT= randomized study; retro cohort=retrospective cohort

\* Very small immunogenicity study (total n=99 which included PCR-confirmed influenza-like illness as an exploratory outcome.

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# HD-IIV3 vs aIIV3: Benefits

Outcome	Studies, n Design	Seasons	Relative Risk†/Rate Ratio§	Importance	Certainty
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Influenza outpatient/ER visits	3 retro cohort§	2	1.06 (0.92, 1.21)	Critical	Level 2 Low
Influenza hospitalizations	4 retro cohort§	4	0.96 (0.90, 1.01)	Critical	Level 3 Low
Influenza deaths	No studies				

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Influenza hospitalizations	4 retro cohort§	4	0.96 (0.90, 1.01)	Critical	Level 3 Low
Influenza deaths	No studies				

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## HD-IIV3 vs aIIV3 : Harms

Outcome	Studies, n Design	Relative Risk†/Rate Ratio§	Importance	Certainty
Any SAE	2 RCT	0.62 (0.24, 1.61)	Important	Level 3 Low
Any solicited injection site AE Grade $\geq 3$	2 RCT†	1.28 (0.64, 2.55)	Important	Level 3 Low
Any solicited systemic AE Grade $\geq 3$	2 RCT†	1.11 (0.45, 2.75)	Critical	Level 3 Low
Guillain-Barré syndrome	1 RCT†	Not estimable	Critical	Level 3 Low

RCT= randomized study; retro cohort=retrospective cohort

† person-time denominator

§ person denominator



## HD-IIV3 vs aIIV3 : Harms

Outcome	Studies, n Design	Relative Risk†/Rate Ratio§	Importance	Certainty
Any SAE	2 RCT†	0.62 (0.24, 1.61)	Important	Level 3 Low
Any solicited injection site AE Grade $\geq 3$	2 RCT†	1.28 (0.64, 2.55)	Important	Level 3 Low
Any solicited systemic AE Grade $\geq 3$	2 RCT†	1.11 (0.45, 2.75)	Critical	Level 3 Low
Guillain-Barré syndrome	1 RCT†	Not estimable	Critical	Level 3 Low

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## HD-IIV3 vs aIIV3 : Harms

Outcome	Studies, n Design	Relative Risk†/Rate Ratio§	Importance	Certainty
Any SAE	2 RCT†	0.62 (0.24, 1.61)	Important	Level 3 Low
Any solicited injection site AE Grade $\geq 3$	2 RCT†	1.28 (0.64, 2.55)	Important	Level 3 Low
Any solicited systemic AE Grade $\geq 3$	2 RCT†	1.11 (0.45, 2.75)	Critical	Level 3 Low
Guillain-Barré syndrome	1 RCT†	Not estimable	Critical	Level 3 Low

RCT= randomized study; retro cohort=retrospective cohort

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- Comparison 1: HD-IIV vs SD-IIV
- Comparison 2: aIIV vs SD-IIV
- Comparison 3: RIV vs SD-IIV
  
- Comparison 4: HD-IIV3 vs aIIV3
- **Comparison 5: HD-IIV3 vs RIV4**
- Comparison 6: aIIV3 vs RIV4

# HD-IIV3 vs RIV: Benefits

Outcome	Studies, n Design	Seasons	Relative Risk†/Rate Ratio§	Importance	Quality
Influenza illnesses	1 RCT*†	1	0.26 (0.03, 2.18)	Critical	Level 4 Very low
Influenza outpatient/ER visits	No studies				
Influenza hospitalizations	1 retro cohort§	1	1.12 (1.03, 1.21)	Critical	Level 2 Moderate
Influenza deaths	No studies				

RCT= randomized study; retro cohort=retrospective cohort

\* Very small immunogenicity study (total n=99 which included PCR-confirmed influenza-like illness as an exploratory outcome.

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# HD-IIV3 vs RIV: Benefits

Outcome	Studies, n Design	Seasons	Relative Risk†/Rate Ratio§	Importance	Quality
Influenza illnesses	1 RCT*†	1	0.26 (0.03, 2.18)	Critical	Level 4 Very low
Influenza outpatient/ER visits	No studies				
Influenza hospitalizations	1 retro cohort§	1	<b>1.12 (1.03, 1.21)</b>	Critical	Level 2 Moderate
Influenza deaths	No studies				

RCT= randomized study; retro cohort=retrospective cohort

\* Very small immunogenicity study (total n=99 which included PCR-confirmed influenza-like illness as an exploratory outcome.

† person denominator

§ person-time denominator

# HD-IIV3 vs RIV: Harms

Outcome	Studies, n Design	Relative Risk†/ Rate Ratio§	Importance	Quality
Any SAE	2 RCT‡	1.77 (0.73, 4.28)	Important	Level 3 Low
Any solicited injection site AE Grade $\geq 3$	2 RCT†	5.92 (0.32, 109.56)	Important	Level 3 Low
Any solicited systemic AE Grade $\geq 3$	2 RCT†	0.83 (0.16, 4.41)	Critical	Level 3 Low
Guillain-Barré syndrome	No studies			

RCT= randomized study; retro cohort=retrospective cohort

† person denominator

§ person-time denominator

- Comparison 1: HD-IIV vs SD-IIV
- Comparison 2: aIIV vs SD-IIV
- Comparison 3: RIV vs SD-IIV
  
- Comparison 4: HD-IIV3 vs aIIV3
- Comparison 5: HD-IIV3 vs RIV4
- **Comparison 6: aIIV3 vs RIV4**

# aIV3 vs RIV4: Benefits

Outcome	Studies, n Design	Seasons	Relative Risk†/Rate Ratio§	Importance	Quality
Influenza illnesses	1 RCT†*	1	0.75 (0.18, 3.07)	Critical	Level 4 Very low
Influenza outpatient/ER visits	No studies				
Influenza hospitalizations	1 retro cohort§	1	1.12 (1.03, 1.22)	Critical	Level 2 Moderate
Influenza deaths	No studies				

RCT= randomized study; retro cohort=retrospective cohort

\* Very small immunogenicity study (total n=99) which included PCR confirmed influenza-like illness as an exploratory outcome.

† person denominator

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# aIV3 vs RIV4: Benefits

Outcome	Studies, n Design	Seasons	Relative Risk†/Rate Ratio§	Importance	Quality
Influenza illnesses	RCT†*	1	0.75 (0.18, 3.07)	Critical	Level 4 Very low
Influenza outpatient/ER visits	No studies				
Influenza hospitalizations	1 retro cohort§	1	<b>1.12 (1.03, 1.22)</b>	Critical	Level 2 Moderate
Influenza deaths	No studies				

RCT= randomized study; retro cohort=retrospective cohort

\* Very small immunogenicity study (total n=99) which included PCR confirmed influenza-like illness as an exploratory outcome.

† person denominator

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## aIIV3 vs RIV4 : Harms

Outcome	Studies, n Design	Relative Risk†/Rate Ratio§	Importance	Quality
Any SAE	1 RCT‡	1.81 (0.58, 5.65)	Important	Level 3 Low
Any solicited injection site AE Grade $\geq 3$	1 RCT†	4.62 (0.24, 89.17)	Important	Level 3 Low
Any solicited systemic AE Grade $\geq 3$	1 RCT†	4.62 (0.24, 89.17)	Critical	Level 3 Low
Guillain-Barré syndrome	No studies			

RCT= randomized study; retro cohort=retrospective cohort

† person denominator

§ person-time denominator

# Evidence Summary: EIVs vs SD-IIVs

Outcome	Importance	HD-IIV3 vs SD-IIV	aIIV3 vs SD-IIV	RIV vs SD-IIV
<b>Benefits</b>				
Influenza illnesses	Critical	Level 1 (High) <b>Favors HD-IIV3</b>	Level 2 (Moderate)	Level 2 (Moderate)
Influenza outpatient/ER visits	Critical	Level 2 (Moderate) <b>Favors HD-IIV3</b>	Level 2 (Moderate)	
Influenza hospitalizations	Critical	Level 2 (Moderate) <b>Favors HD-IIV3</b>	Level 2 (Moderate) <b>Favors aIIV3</b>	Level 2 (Moderate) <b>Favors RIV4</b>
Influenza deaths	Critical	Level 2 (Moderate) <b>Favors HD-IIV3</b>		
<b>Harms</b>				
Any Serious Adverse Event (SAE)	Important	Level 1 (High) <b>Favors HD-IIV3</b>	Level 2 (Moderate)	Level 3 (Low)
Solicited injection site adverse events Grade ≥3	Important	Level 3 (Low)	Level 3 (Low) <b>Favors SD-IIV</b>	Level 3 (Low)
Solicited systemic adverse events Grade ≥3	Critical	Level 3 (Low)	Level 3 (Low)	Level 3 (Low)
Guillain-Barré syndrome	Critical	Level 3 (Low)	Level 3 (Low)	Level 4 (Very low)
<b>OVERALL CERTAINTY</b>		<b>Level 3 (Low)</b>	<b>Level 3 (Low)</b>	<b>Level 4 (Very low)</b>

# Evidence Summary: EIVs vs One Another

Outcome	Importance	HD-IIV3 vs aIIV3	HD-IIV3 vs RIV	aIIV3 vs RIV
<b>Benefits</b>				
Influenza illnesses	Critical	Level 4 (Very low)	Level 4 (Very low)	Level 4 (Very low)
Influenza outpatient/ER visits	Critical	Level 2 (Low)		
Influenza hospitalizations	Critical	Level 3 (Low)	Level 2 (Moderate) <b>Favors RIV4 (1 retro cohort study)</b>	Level 2 (Moderate) <b>Favors RIV4 (1 retro cohort study)</b>
Influenza deaths	Critical			
<b>Harms</b>				
Any Serious Adverse Event (SAE)	Important	Level 3 (Low)	Level 3 (Low)	Level 3 (Low)
Solicited injection site adverse events Grade ≥3	Important	Level 4 (Low)	Level 3 (Low)	Level 3 (Low)
Solicited systemic adverse events Grade ≥3	Critical	Level 3 (Low)	Level 3 (Low)	Level 3 (Low)
Guillain-Barré syndrome	Critical	Level 3 (Low)		
<b>OVERALL CERTAINTY</b>		<b>Level 4 (Very low)</b>	<b>Level 4 (Very low)</b>	<b>Level 4 (Very low)</b>

# Overall Summary: EIVs vs SD-IIVs

- Limited RCT data
- High quality evidence favoring HD-IIV3 over SD-IIV from 1 RCT
- From observational data, overall Moderate certainty favoring each EIV over SD-IIVs against influenza-related hospitalizations
  - Limitations of these data include that most are large retrospective cohort studies for which outcomes are defined by diagnostic codes rather than laboratory confirmed influenza.
  - The largest quantity of data are available for HD-IIV3, less for aIIV3, and least (1 study) for RIV.
- Few differences in safety outcomes overall (and none for critical outcomes)

# Overall Summary: EIVs vs One Another

- Very limited, Very low certainty RCT data
- From Observational data, Moderate quality evidence favoring RIV4 over HD-IIV3 and aIIV3 against hospitalization,
  - However, this is from one retrospective cohort study conducted over a single season.
- No safety differences among the three EIV comparisons.
- Overall, evidence providing direct comparisons of EIVs with one another does not indicate superiority of one over the others.

# Conclusions

- Overall, there is evidence of benefit favoring each EIV over ~~SDs~~
  - Most evidence for HD-IIV3
  - Fewer studies and no RCT including lab-confirmed outcomes for aIIV3
  - Fewest studies for RIV
- No strong evidence favoring one EIV over others among studies providing direct comparisons.
- Limitations include:
  - Few RCT data overall, representing few influenza seasons.
  - No data reflecting currently available formulations of HD-IIV and aIIV (which are now quadrivalents--HD-IIV4 and aIIV4)
    - Prelicensure studies have generally indicated similar immunogenicity of quadrivalent vaccines and their trivalent counterparts

***Thank You!***





Supplemental slides

# Systematic Review Methods Overview

- Databases searched: Medline, Embase, CINAHL, Scopus, Cochrane Library, ClinicalTrials.gov
- Publication dates from 1990 forward: no language restriction
- Literature search last updated September 9, 2021.
- Bibliographies of citations selected for full-text review hand searched to find additional citations.
- Two reviewers independently performed title/abstract screens, full-text reviews, data abstraction, and risk of bias assessments.
- Risk of bias assessment employed
  - Cochrane Risk of Bias tool for randomized studies.<sup>1</sup>
  - Risk of Bias for Nonrandomized Studies of Interventions (ROBINS-I) for observational studies.<sup>2</sup>

<sup>1</sup> Higgins JPT et al, BMJ 2011;343:d5928

<sup>2</sup> Sterne JAC et al. BMJ 2016; 355; i4919; doi: 10.1136/bmj.i4919.

# Systematic Review Inclusion/Exclusion Criteria

- Focus on published/peer-reviewed primary source literature.
  - Abstracts, clinical trial registry summaries, and review articles not included, but used to identify additional citations.
- Main inclusion criteria:
  - Randomized studies (individually- and cluster-randomized designs).
  - Retrospective case-control studies (traditional and test-negative designs).
  - Retrospective and prospective cohort studies.
- Main exclusion criteria:
  - Data involving influenza vaccines not licensed/available in the United States for persons  $\geq 65$  years of age.
  - Studies/data for which the entire population falls outside age range of interest
  - Studies/data assessing monovalent or bivalent vaccines.
  - Case series, case reports, registry reports without comparator or denominator information.
  - Animal studies.
  - Interim reports superseded by final reports.

# PRISMA Diagram

