High Dose vs. Standard Dose Inactivated Influenza Vaccine for Older Adults—Update on GRADE Process

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Influenza WG

Background

- **High Dose Inactivated Influenza Vaccine (HD-IIV; Fluzone®High-Dose, Sanofi Pasteur) approved in 2009**
  - Superior immunogenicity compared with standard dose IIV (SD-IIV) for persons ≥65 years of age
- **Large randomized controlled comparative trial conducted over 2011-12 and 2012-13 seasons**
  - 24.2% relative efficacy of HD- vs. SD-IIV for prevention of laboratory-confirmed influenza associated with a protocol-defined influenza-like illness (ILI) among persons ≥65 years of age
- **ACIP recommendations state that either HD- or SD-IIV are appropriate options for persons ≥65 years of age**

DiazGranados CA, et al, N Engl J Med 2014; 371: 635-45

Question Assessed

- **Do benefits and harms favor HD-IIV vs. SD-IIV for adults 65 years and older?**
  - i.e., better efficacy in preventing outcomes of interest
  - comparable safety profile

- **Framing the question:**
  - Population: adults 65 years of age and older
  - Intervention: HD-IIV
  - Comparison: SD-IIV
  - Outcomes
    - Potential effectiveness & safety outcomes generated by Influenza WG
    - Safety outcomes discussed with CISA for input
    - Rated in terms of importance to policymaking decisions
      - 7 - 9 = Critical, 4 - 6 = Important, 1 - 3 = Not Important

HD-IIV vs. SD-IIV: EFFICACY

HD-IIV vs. SD-IIV—Efficacy Outcomes

Efficacy Outcomes	# of RCTs	Data Sources
Critical		
Any LCI	2	DiazGranados 2013, 2014
LCI-associated hospitalization	1	DiazGranados 2014
LCI-associated pneumonia	1	DiazGranados 2014
Medically attended LCI	1	DiazGranados 2014
LCI-associated ED visit	1	DiazGranados 2014
Important		
MAARI	1	DiazGranados 2014
Any influenza-like illness	2	DiazGranados 2013, 2014

No information for these 13 outcomes:

- CRITICAL: LCI-associated death
- IMPORTANT: All-cause deaths, ED visits, hospitalizations, and pneumonia; Basic activities of daily living; Catastrophic disability; Cognition; Delirium; Depression; Frailty; Loss of independence; Loss of mobility

Abbreviations: ED = Emergency department; LCI = Laboratory-confirmed influenza; MAARI = Medically attended acute respiratory illness; RCT = randomized controlled trial

Summary for Efficacy Outcomes: Critical (1)

Outcome	n	Risk of Bias	Inconsistency	Indirectness	Imprecision	Evidence Type	RR [95% CI] Risk Diff. with HD [95% CI]
CRITICAL							
Any LCI, all viral types and subtypes	2* (RCT)	Not serious	Not serious	Not serious	Not serious	1 (High)	0.82 [0.71 - 0.95] 4 fewer per 1000 [1-6 fewer]
Any LCI, all viral types and subtypes, excluding the 2009-10 season	1 (RCT)	Not serious	n/a	Not serious	Not serious	1 (High)	0.82 [0.71 - 0.95] 4 fewer per 1000 [1-7 fewer]

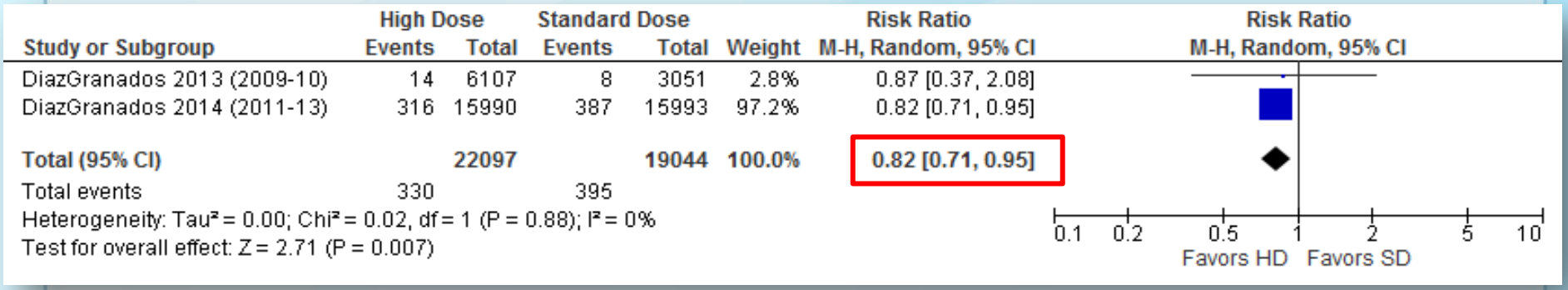
* DiazGranados 2013 and 2014.

† DiazGranados 2014.

HD-IIV vs. SD-IIV
Lab-confirmed Influenza, All Viral Types/Subtypes
(CRITICAL)

# of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Risk Difference with HD [95% CI]	Evidence Type
2	Not Serious	Not Serious	Not Serious	Not Serious	4 fewer per 1000 [1-6 fewer]	1 High

- Any culture- or PCR-confirmed influenza illness caused by any viral type or subtype, among persons with protocol-defined respiratory illness (DiazGranados 2014) or protocol-defined ILI (DiazGranados 2013)



Summary for Efficacy Outcomes: Critical (2)

Outcome	n	Risk of Bias	Inconsistency	Indirectness	Imprecision	Evidence Type	RR [95% CI] Risk Diff. with HD [95% CI]
CRITICAL							
LCI-associated Hospitalizations*	1 (RCT)	Not serious	n/a	Serious†	Serious§	3 (Low)	0.64 [0.25-1.63] *
LCI-associated Pneumonia*	1 (RCT)	Not serious	n/a	Serious†	Serious§	3 (Low)	0.57 [0.17-1.83] *
Medically Attended LCI*	1 (RCT)	Not serious	n/a	Serious†	Not serious	2 (Mod)	0.94 [0.76-1.17] *
LCI-associated ED visits*	1 (RCT)	Not serious	n/a	Serious†	Serious§	3 (Low)	1.42 [0.54-3.71] *

DiazGranados (2014)

* Data reported as events per person–time for these outcomes.

† Downgrade for indirectness: events were any that occurred within 30 days of lab confirmed influenza illness, but not confirmed due to influenza illness.

§ Downgrade for imprecision: 95% confidence interval includes 1.0 and exceeds 0.75 in lower bound and/or 1.25 in upper bound)

HD-IIV vs. SD-IIV: SAFETY

Sources for Safety Data

Outcome	n	Data Sources
Critical		
AE causing study discontinuation	5 (RCT)	DiazGranados 2013, 2014, Falsey 2009, Keitel 2006, Tsang 2014
Any related SAE	7 (RCT)	Couch 2007, DiazGranados 2013, 2014, Falsey 2009, Keitel 2006, Nace 2014, Tsang 2014
Important		
Any SAE	7 (RCT)	Couch 2007, DiazGranados 2013, 2014, Falsey 2009, Keitel 2006, Nace 2014, Tsang 2014
Any death	6 (RCT)	Couch 2007, DiazGranados 2013, 2014, Falsey 2009, Keitel 2006, Nace 2014
Fever (any grade)	2 (RCT)	Couch 2007, Falsey 2009
Myalgia (grade ≥2)	2 (RCT)	
Headache (grade ≥2)	2 (RCT)	
Malaise or fatigue (grade ≥2)	2 (RCT)	
Local swelling/induration (grade ≥2)	2 (RCT)	
Local pain (grade ≥2)	2 (RCT)	

No information for:

CRITICAL: Immediate hypersensitivity/anaphylaxis; IMPORTANT: Arthralgia; nausea/vomiting

Summary for Safety Outcomes--Critical

Outcome	n	Risk of Bias	Inconsistency	Indirectness	Imprecision	Evidence Type	RR [95% CI] Risk Diff. with HD [95% CI]
CRITICAL							
AE causing study discontinuation	5 (4)*	Not serious	Not serious	Not serious	Serious§	2 (Mod)	0.92 [0.73-1.15] 1 fewer per 1000 [2 fewer-1 more]
Any related SAE	7 (3)*	Not serious	Not serious	Not serious	Serious§	2 (Mod)	0.96 [0.19-4.88] 0 fewer per 1000 [0 fewer-1 more]
Immediate hypersensitivity or anaphylaxis	0	n/a†				n/a	n/a

* Some studies reported an event count of 0 and so do not contribute to risk calculations. Number in parentheses represents studies having at ≥1 event.

† Immediate hypersensitivity/anaphylaxis not reported for any study.

§ Downgrade for imprecision: 95% confidence interval includes 1.0 and exceeds 0.75 in lower bound and/or 1.25 in upper bound)

Summary of Findings for Safety Outcomes—Important (1)

Outcome	n	Risk of Bias	Inconsistency	Indirectness	Imprecision	Evidence Type	RR [95% CI] Risk Diff. with HD [95% CI]
IMPORTANT							
Any SAE	7 (RCT)	Not serious	Not serious	Not serious	Not serious	1 (High)	0.96 [0.90-1.02] 3 fewer per 1000 [8 fewer-2 more]
Any death, within 6 months	6 (5)* (RCT)	Not serious	Not serious	Not serious	Serious†	2 (Mod)	1.03 [0.79-1.33] 0 more per 1000 [1 fewer-2 more]
Any death, within 30 days	2 (1)* (RCT)	Not serious	Not serious	Not serious	Very† serious	3 (Low)	13.0 [0.73-230.73] Not estimable

* Some studies reported an event count of 0 and so do not contribute to risk calculations. Number in parentheses represents studies having at ≥1 event.

† Downgrade for imprecision: 95% confidence interval includes 1.0 and exceeds 0.75 in lower bound and/or 1.25 in upper bound)

Summary of Findings for Safety Outcomes—Important (2)

Outcome	n	Risk of Bias	Inconsistency	Indirectness	Imprecision	Evidence Type	RR [95% CI] Risk Diff. with HD [95% CI]
IMPORTANT							
Fever, any grade	2 (RCT)	Not serious	Not serious	Not serious	Serious	2 (Mod)	2.81 [0.55-14.40] 37 more per 1000 (9 fewer-274 more]
Myalgia, grade ≥2	2 (RCT)	Not serious	Not serious	Not serious	Serious*	2 (Mod)	2.37 [0.93-6.01] 43 more per 1000 [2 fewer-157 more]
Headache, grade ≥2	2 (RCT)	Not serious	Not serious	Not serious	Not serious	1 (High)	1.51 [1.06-2.15] 14 more per 1000 [2-31 more]
Malaise or fatigue, grade ≥2	2 (RCT)	Not serious	Not serious	Not serious	Not Serious	1 (High)	1.55 [1.16-2.07] 22 more per 1000 [6-42 more]

* Downgrade for imprecision: 95% confidence interval includes 1.0 and exceeds 0.75 in lower bound and/or 1.25 in upper bound)

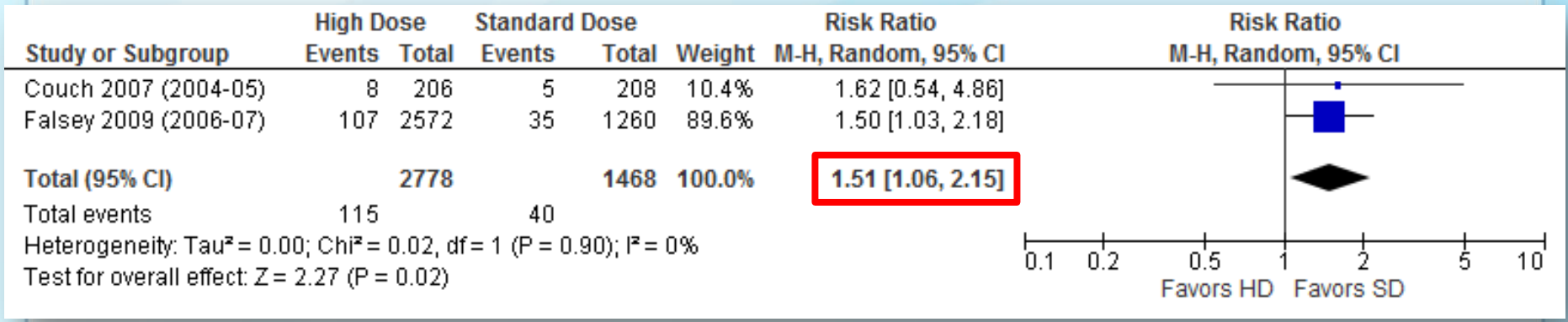
Summary of Findings for Safety Outcomes—Important (3)

Outcome	n	Risk of Bias	Inconsistency	Indirectness	Imprecision	Evidence Type	RR [95% CI] Risk Diff. with HD [95% CI]
IMPORTANT (continued)							
Local swelling or induration, grade ≥2	2 (RCT)	Not serious	Not serious	Not serious	Not Serious	1 (High)	1.61 [1.08-2.40] 13 more per 1000 [2-31 more]
Local Pain or tenderness, grade ≥2	2 (RCT)	Not serious	Not serious	Not serious	Serious	2 (Mod)	2.13 [0.88-5.15] 19 more per 1000 (2 fewer-70 more]

* Downgrade for imprecision: 95% confidence interval includes 1.0 and exceeds 0.75 in lower bound and/or 1.25 in upper bound)

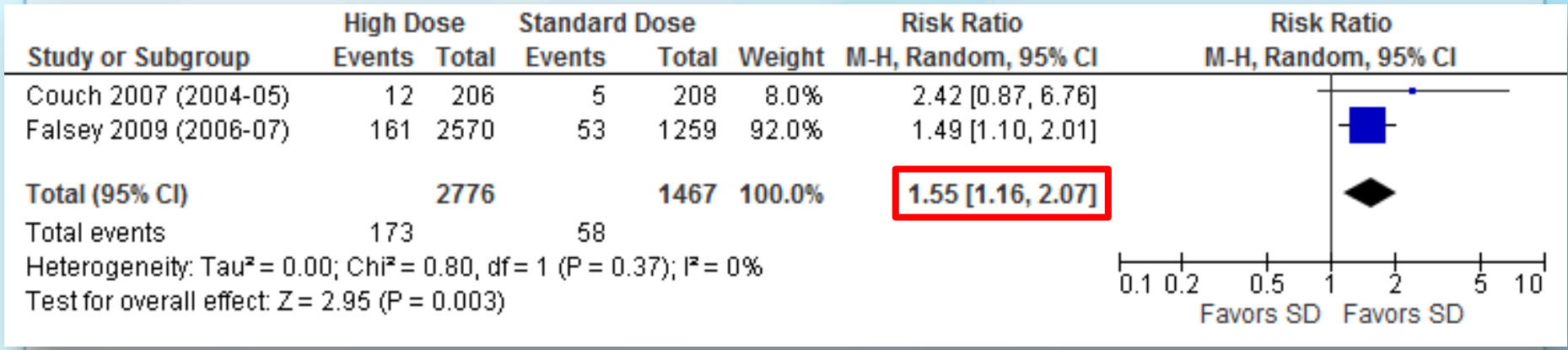
HD-IIV vs. SD-IIV Headaches, Grade ≥2 (IMPORTANT)

# of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Risk Difference with HD [95% CI]	Evidence Type
2	Not serious	Not serious	Not serious	Not Serious	14 more per 1000 [2-31 more]	1 High



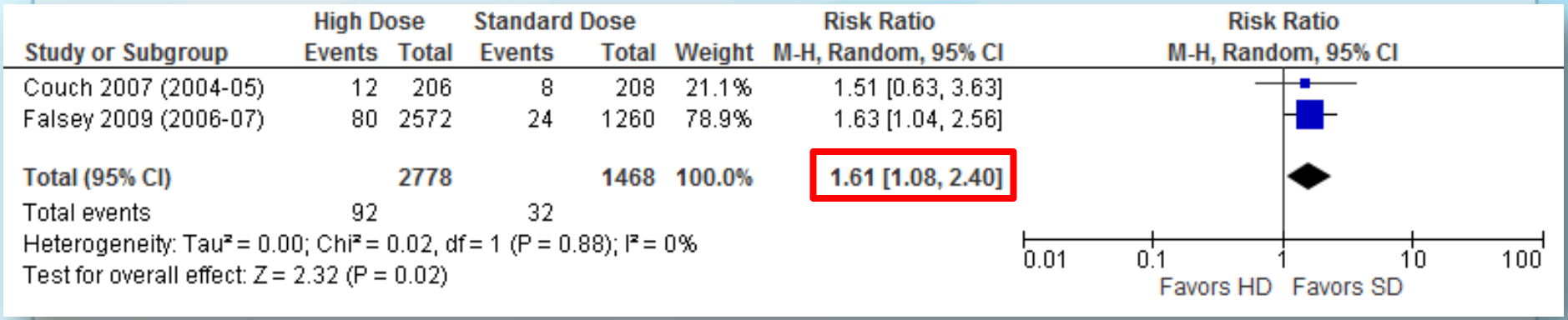
HD-IIV vs. SD-IIV
Malaise or Fatigue, Grade ≥2 (IMPORTANT)

# of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Risk Difference with HD [95% CI]	Evidence Type
2	Not serious	Not serious	Not serious	Not serious	22 more per 1000 [6-42 more]	1 High



HD-IIV vs. SD-IIV
Local Swelling or Induration, Grade ≥2 (IMPORTANT)

# of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Risk Difference with HD [95% CI]	Evidence Type
2	Not serious	Not serious	Not serious	Not Serious	13 more per 1000 [2-31 more]	1 High



Critical Outcome Summary

Outcome (Importance)	RCTs, n	Findings	Evidence Type	Overall Evidence Type
EFFICACY/EFFECTIVENESS				3 (Low)
Any lab confirmed influenza	2	Lower risk with HD RR: 0.82 (0.71 - 0.95) RD 4 fewer per 1000 (1-6 fewer)	1 (High)	
LCI-associated hospitalization	1	No difference	3 (Low)	
LCI-associated pneumonia	1	No difference	3 (Low)	
Medically attended LCI	1	No difference	2 (Moderate)	
LCI-associated ED visits	1	No difference	3 (Low)	
LCI-associated deaths	None	-	-	
SAFETY				
AE causing study discontinuation	5 (4)	No difference	2 (Moderate)	
Any related SAE	7 (3)	No difference	2 (Moderate)	
Immediate hypersensitivity/anaphylaxis	None	-	-	

Limitations

- Main source for efficacy outcomes is a single study conducted over two seasons
- Data for some "Critical" outcomes are not available (LCI-associated deaths, anaphylaxis), or available data are indirect (LCI-associated severe clinical outcomes)
  - However, potentially difficult to power an RCT for these outcomes
- Some safety outcomes of interest very uncommon
  - Again, may be difficult to power for some of these outcomes
- Safety outcomes may not have been defined or interpreted similarly across studies

Additional Study—Izurieta et al, 2015

- Retrospective cohort study of Medicare beneficiaries 65 and older who received HD-IIV or SD-IIV during the 2012-13 season
- Primary outcome: probable influenza infection
  - Receipt of rapid influenza test followed by dispensing of oseltamivir
- Secondary outcome: hospital or emergency department visit, listing a Medicare billing code for influenza.
- Among 929,730 HD recipients and 1,615,545 SD recipients identified, HD-IIV was
  - 22% (95%CI 15-29) more effective in preventing probable influenza;
  - 22% (95%CI 16-27) more effective in preventing influenza hospital admission
- Not included in GRADE--felt not to address critical/important outcome

Izurieta HS, et al, Lancet Infect Dis, online February 9, 2015

Fluzone High-Dose® post-licensure safety data from initial influenza season of use (2010-11)

- Moro et al. Postlicensure safety surveillance for high-dose trivalent inactivated influenza vaccine in the Vaccine Adverse Event Reporting System, 1 July 2010-31 December 2010. Clin Infect Dis. 2012;54(11):1608-14.
  - 606 reports in persons aged ≥65 years (8.2% serious)
  - MedDRA[a] terms for "ocular hyperemia" and "vomiting" exceeded the data mining threshold [b] (80% non-serious)
  - Clinical review of serious reports found a greater proportion of gastrointestinal events (5/51 [9.8%]) compared to IIV3 (1/123 [0.8%])
  - During the first year after US licensure of TIV-HD, no new serious safety concerns were identified in VAERS. Analyses suggested a clinically important imbalance between the reported and expected number of gastrointestinal events after TIV-HD receipt.

[a] MedDRA: Medical Dictionary for Regulatory Activities
[b] Lower bound of 90% CI (EB05) > 2

Fluzone High-Dose® post-licensure safety data from 2011-2015

- Disproportional reporting for MedDRA[a] term "vomiting" observed during 2012-2013 season
- Most vomiting reports non-serious and self-limited
- Disproportional reporting for MedDRA[a] term "drug administered to patient of inappropriate age" observed during 2012-2013 and 2013-2014 seasons
- No new safety concerns identified in VAERS reporting for Fluzone High-Dose® in monitoring from 2011-15, following its initial season of use

[a] MedDRA: Medical Dictionary for Regulatory Activities

Thank You!

For more information please contact Centers for Disease Control and Prevention

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