

Overview of US LAIV Policy

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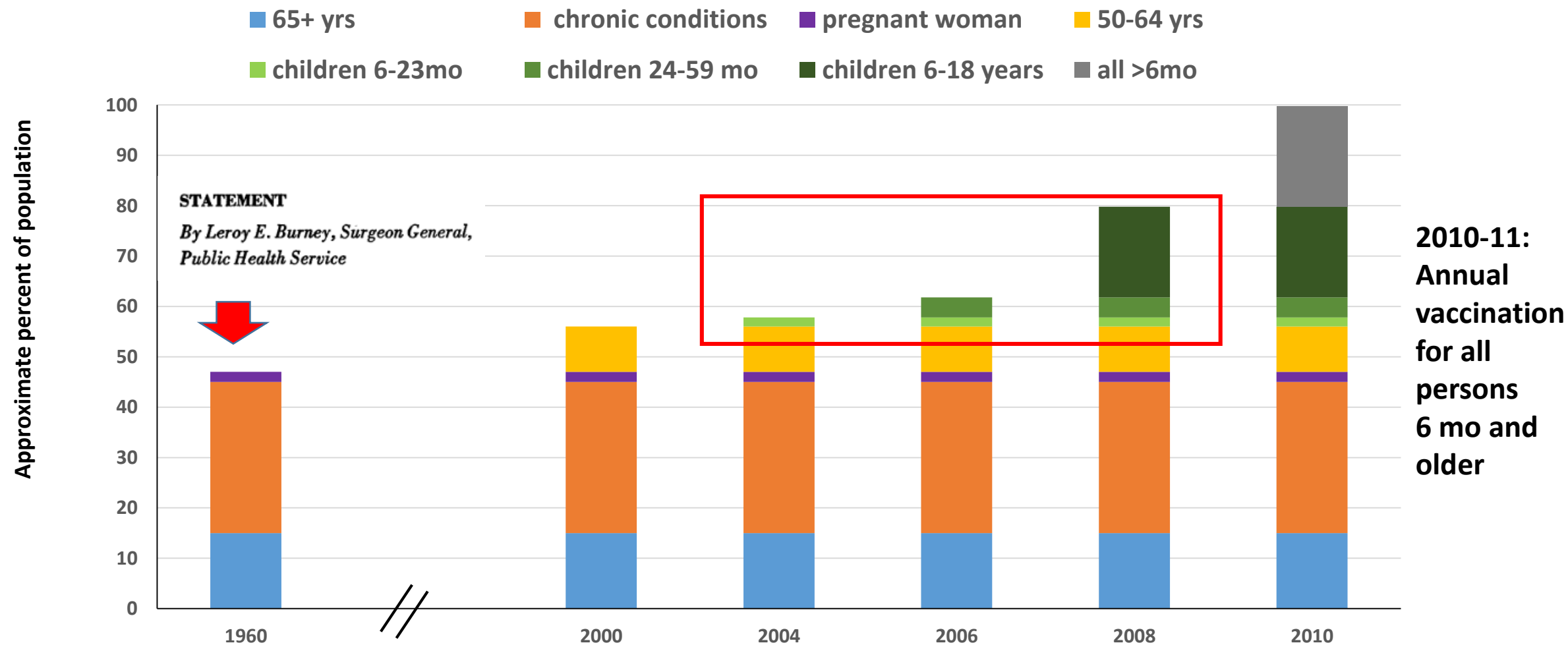
Chief , Epidemiology and Prevention Branch

Influenza Division, CDC

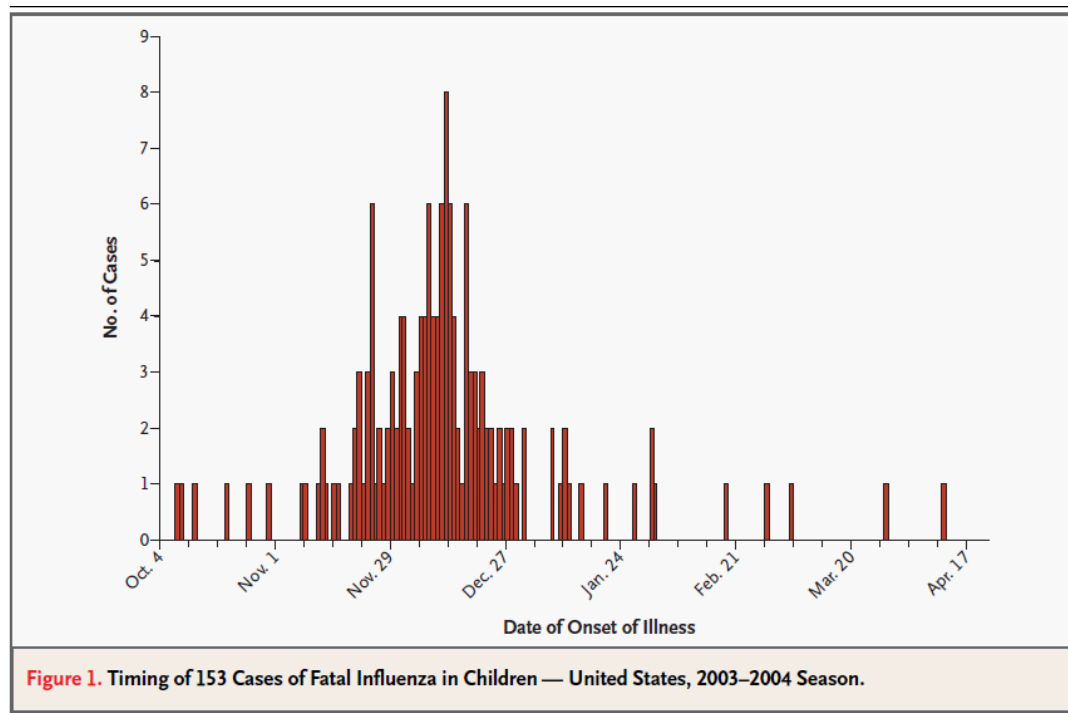
Australia Immunisation Coalition Meeting

Feb 3, 2019

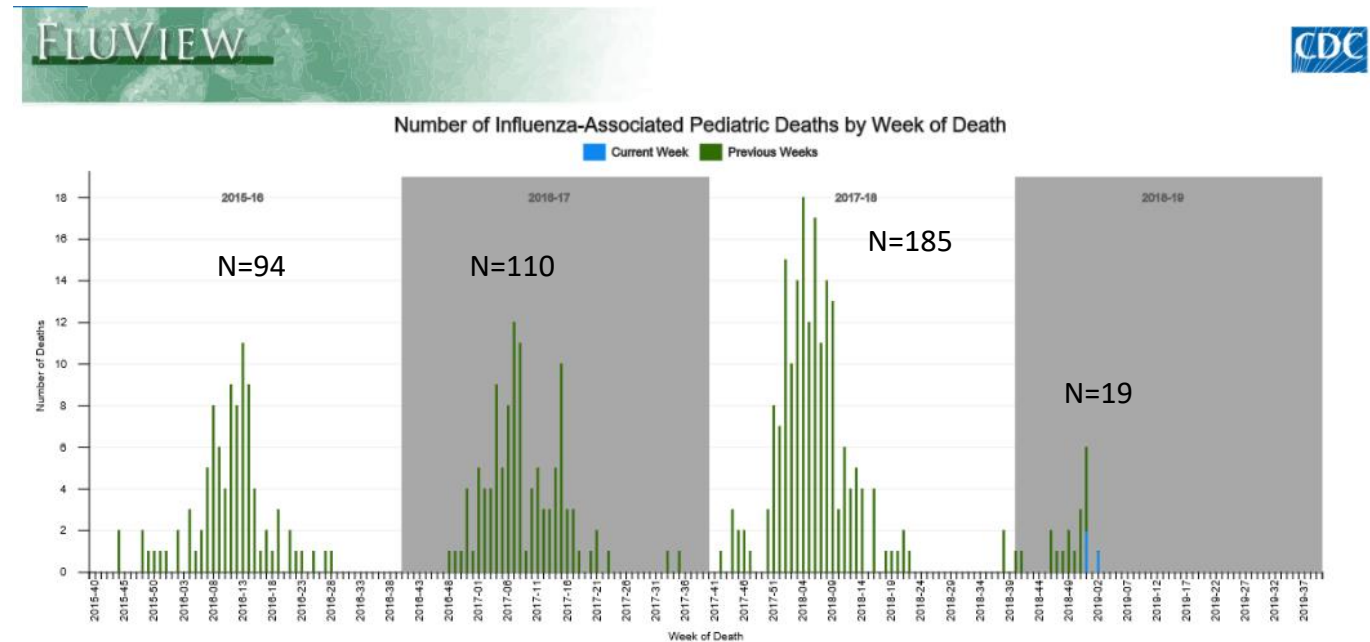
US Recommendations for influenza vaccination have changed over time



Drivers for pediatric vaccination policy



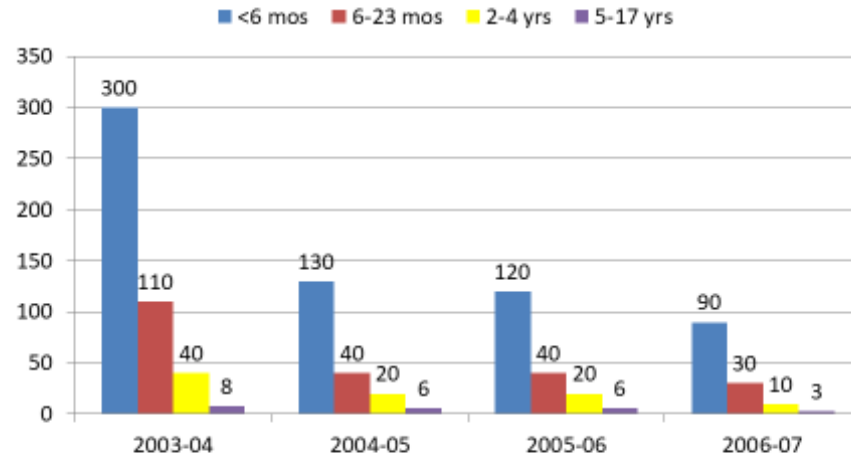
Bhat, et al NEJM 2005



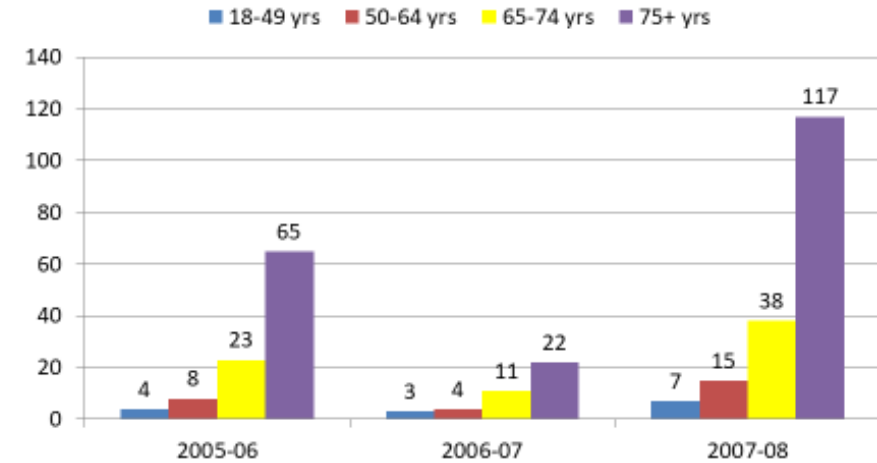
- 50% of deaths have no underlying disease
- Rates inversely correlated with age
- ~80% unvaccinated
- 40% die before admission to the hospital

Drivers for pediatric vaccination policy

Rates of influenza associated hospitalization/100 K in children, 2003-04 to 2007-08, EIP



Rates of influenza associated hospitalization/100 K in adults, 2005-06 to 2007-08, EIP



Vaccine coverage

Figure 1. Flu Vaccination Coverage by Age Group and Season, Children 6 Months—17 years, United States, 2010–2018



US LAIV Policy timeline

LAIV3 licensed
by FDA 5-49 yrs;
ACIP
recommends
for use

LAIV3
licensed for
2-49 yrs;
ACIP
recommends

LAIV4 licensed by
FDA;
ACIP recommends
for use for 2013-14

ACIP preferentially
recommends LAIV (vs
IIV) for healthy 2-8 yrs
for 2014-15

2013-14 Flu season
H1N1pdm09

2003

2007

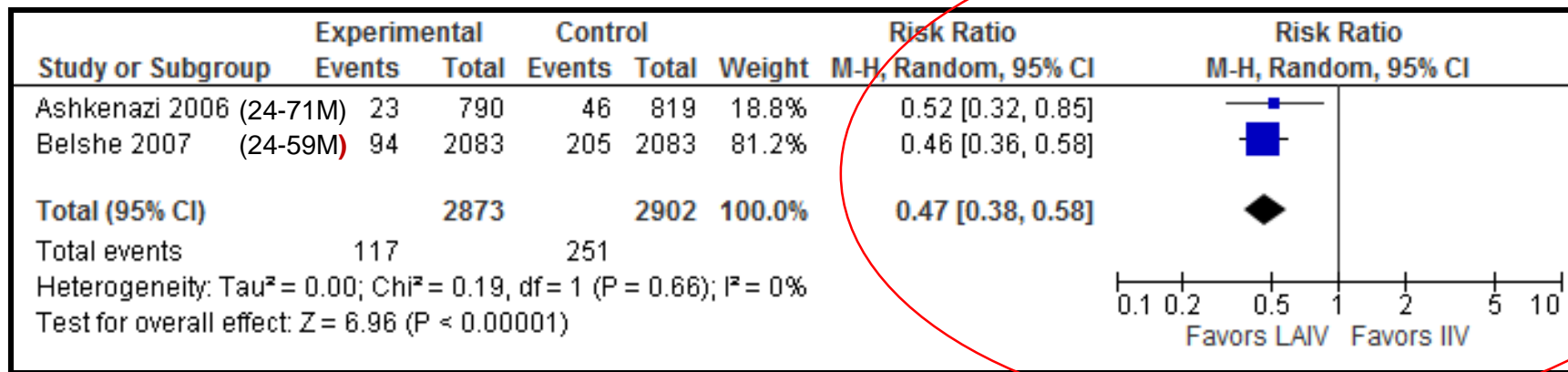
2012

Feb
2014

Evidence Profile—LAIV vs. IIV—2-8-year-olds Lab-confirmed Influenza—Randomized Studies

Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect		Quality
					RR [95% CI]	Risk Difference with LAIV [95% CI]	
2	Not serious	Not Serious	Not Serious	Not Serious	0.47 [0.38 – 0.58]	46 fewer per 1000 [36 – 54 fewer]	1 (High)

- Data from both studies restricted to children aged ≥ 24 months (meta-analysis by Ambrose et al, Vaccine 2012)



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2013-14 final
LAIV and IIV VE
estimates shared
with ACIP

2013-14 Flu season
H1N1pdm09

2003

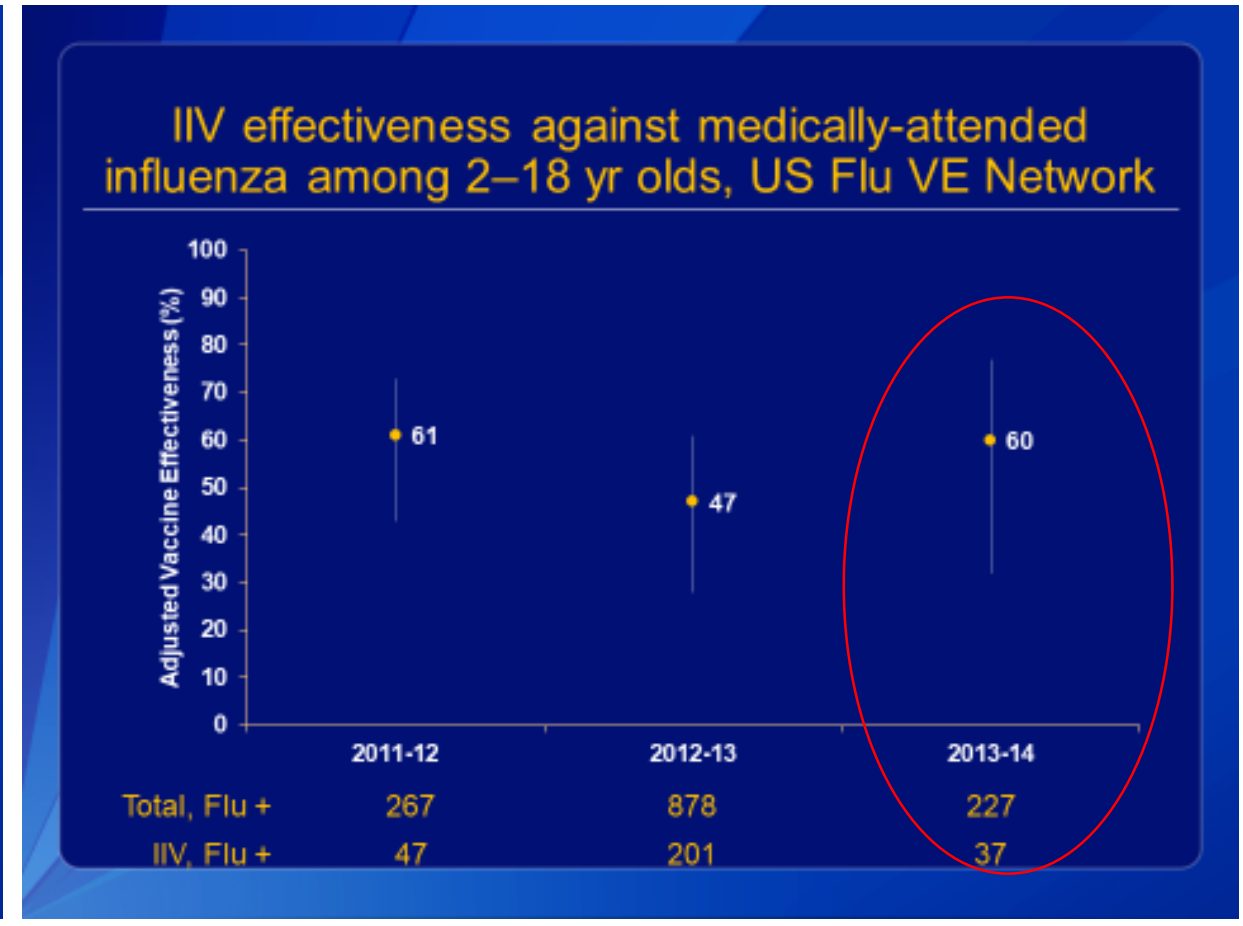
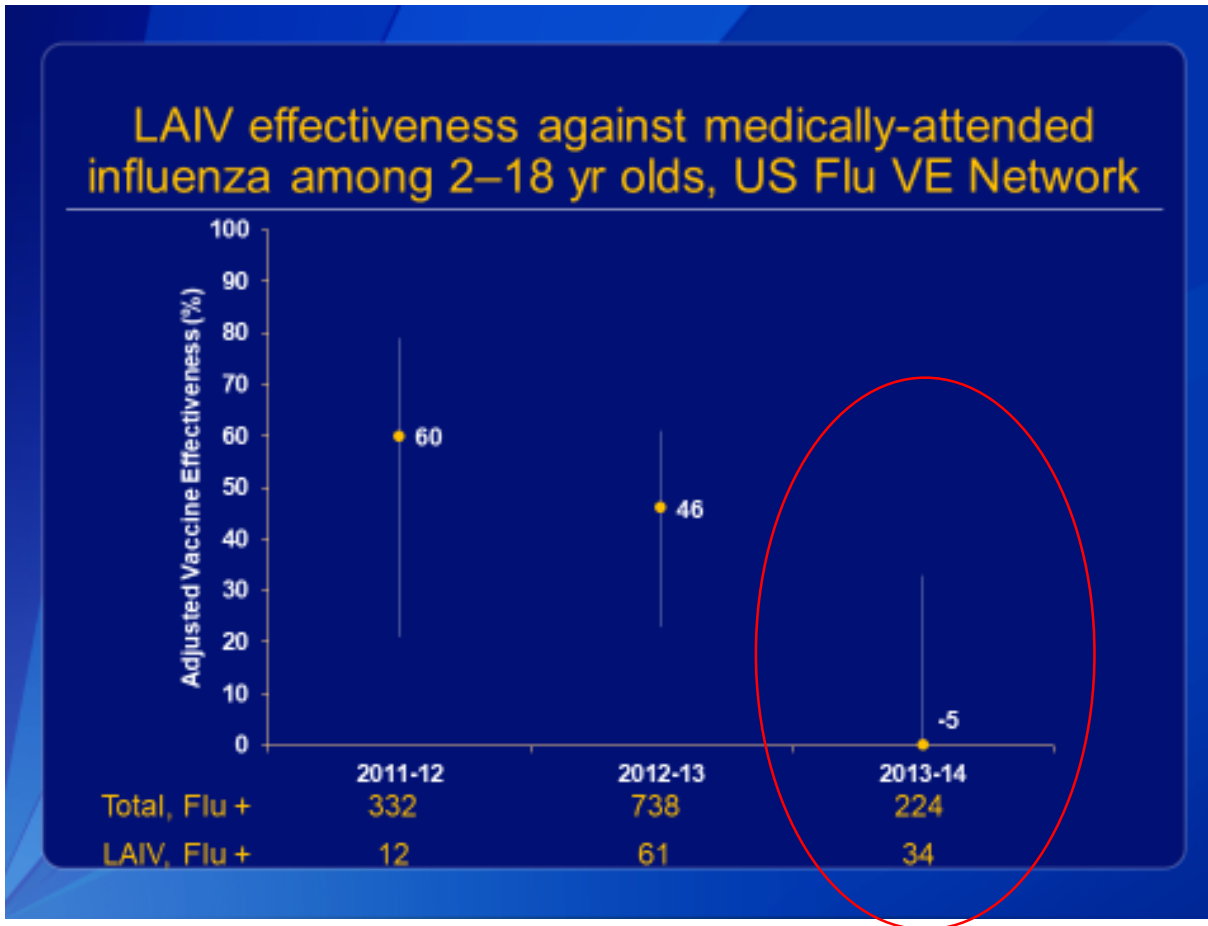
2007

2012

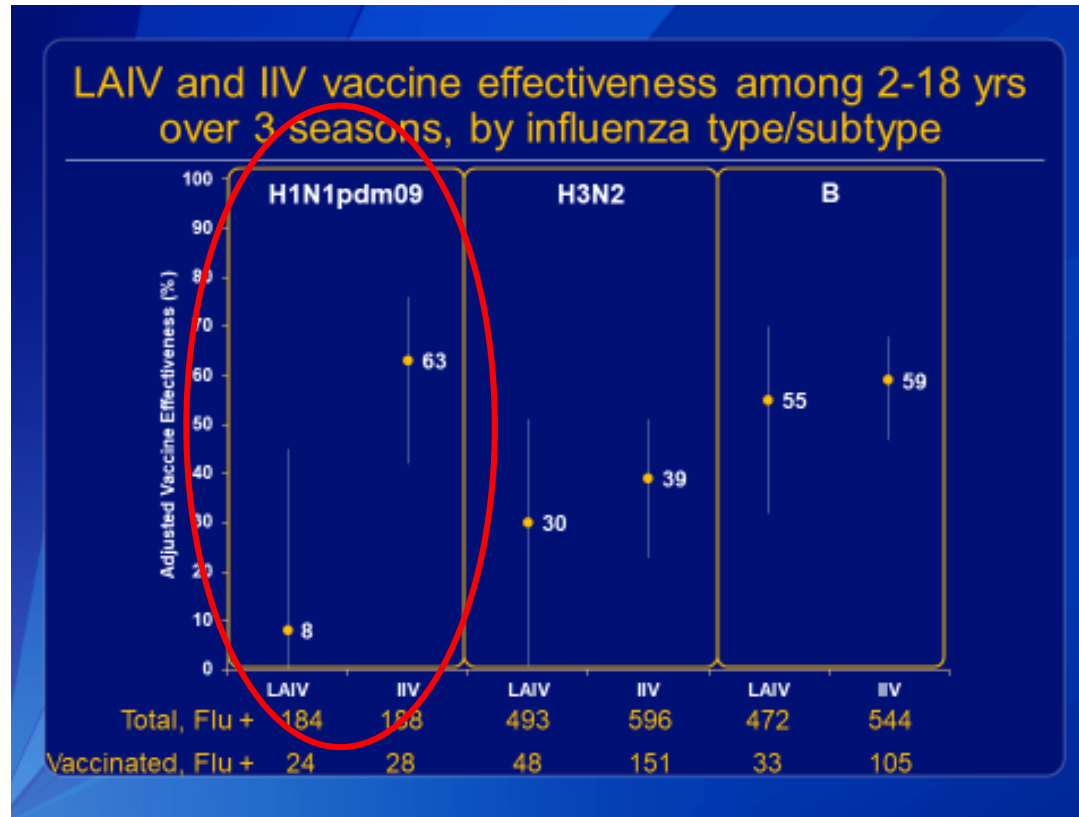
Feb
2014

Oct
2014

During 2013-14 LAIV did not provide protection in children; IIV was protective



H1N1pdm09 LAIV component did not protect



- For 2013-14, Medimmune US ICICLE study and US DoD VE Network found similar findings

US LAIV Policy timeline

ACIP preferentially recommends LAIV (vs IIV) for healthy 2-8 yrs for 2014-15

2013-14 final LAIV and IIV VE estimates shared with ACIP

ACIP removes preference for 2015-16.

2014-15 Interim (mid season) LAIV and IIV VE shared with ACIP

2015-16 LAIV H1 changed to A/Bolivia/H1N1



2013-14 Flu season
H1N1pdm09

Feb
2014

October
2014

2014-15 Flu season
Drifted H3N2

Feb
2015

Pre 2009 RCT data: LAIV VE against mismatch

Table 2. Influenza Attack Rates in the According-to-Protocol Population.*

Variable	Similarity to Vaccine†	Live Attenuated Vaccine (N=3916)‡		Inactivated Vaccine (N=3936)§		Reduction in Attack Rate with Live Vaccine¶
		Cases	Attack Rate	Cases	Attack Rate	
		no.	%	no.	%	
Virus	Well matched	53	1.4	93	2.4	44.5 (22.4 to 60.6)
A/H1N1		3	0.1	27	0.7	89.2 (67.7 to 97.4)
A/H3N2		0	0	0	0	—
B		50	1.3	67	1.7	27.3 (−4.8 to 49.9)
Virus	Not well matched	102	2.6	245	6.2	58.2 (47.4 to 67.0)
A/H1N1		0	0	0	0	—
A/H3N2		37	0.9	178	4.5	79.2 (70.6 to 85.7)
B		66	1.7	71	1.8	6.3 (−31.6 to 33.3)

Interim adjusted VE estimates against A(H3N2) for ≥1 dose of 2014-15 seasonal influenza vaccine among children and adolescents, by vaccine type

	Influenza- positive	% vaccinated	Influenza- negative	% vaccinated	Adjusted VE	[95% CI]
Any vaccine						
2–17 years	519	43%	1103	46%	7%	(-16 to 26)
2–8 yrs	282	45%	691	49%	6%	(-27 to 31)
9–17 yrs	237	39%	414	41%	12%	(-27 to 39)
Live-attenuated (LAIV4)						
2–17 years	383	22%	740	20%	-24%	(-74 to 11)
2–8 yrs	205	25%	451	23%	-23%	(-90 to 21)
9–17 yrs	178	19%	289	15%	-20%	(-115 to 33)
Inactivated (IIV3/IIV4)						
2–17 years	434	31%	957	38%	18%	(-7 to 37)
2–8 yrs	231	33%	589	41%	15%	(-20 to 40)
9–17 yrs	203	29%	368	33%	19%	(-23 to 46)

* Vaccine effectiveness was estimated as 100% X (1 – odds ratio [ratio of odds of vaccination among flu-positive cases to odds of vaccination among flu-negative controls]) using logistic regression. Multivariate models adjusted for study site, age, sex, race/Hispanic ethnicity, self-rated health status, days from illness onset to enrollment, and calendar time (biweekly intervals). Models for "all ages" include age as a categorical variable; age-specific models include age in years as a continuous variable.

**LAIV and IIV
performed
equally
against the
drifted H3N2
3c.2a viruses**

**Confirmed in
two US
observational
studies:
Medimmune
ICICLE and DoD**

US LAIV Policy timeline

ACIP removes preference
for 2015-16.

2014-15 Interim season
LAIV and IIV VE shared
with ACIP

2015-16 LAIV H1 changed
to A/Bolivia/H1N1

ACIP does not recommended
LAIV for 2016-17

2015-16 final season LAIV
and IIV VE shared with
ACIP



2014-15 Flu season
Drifted H3N2

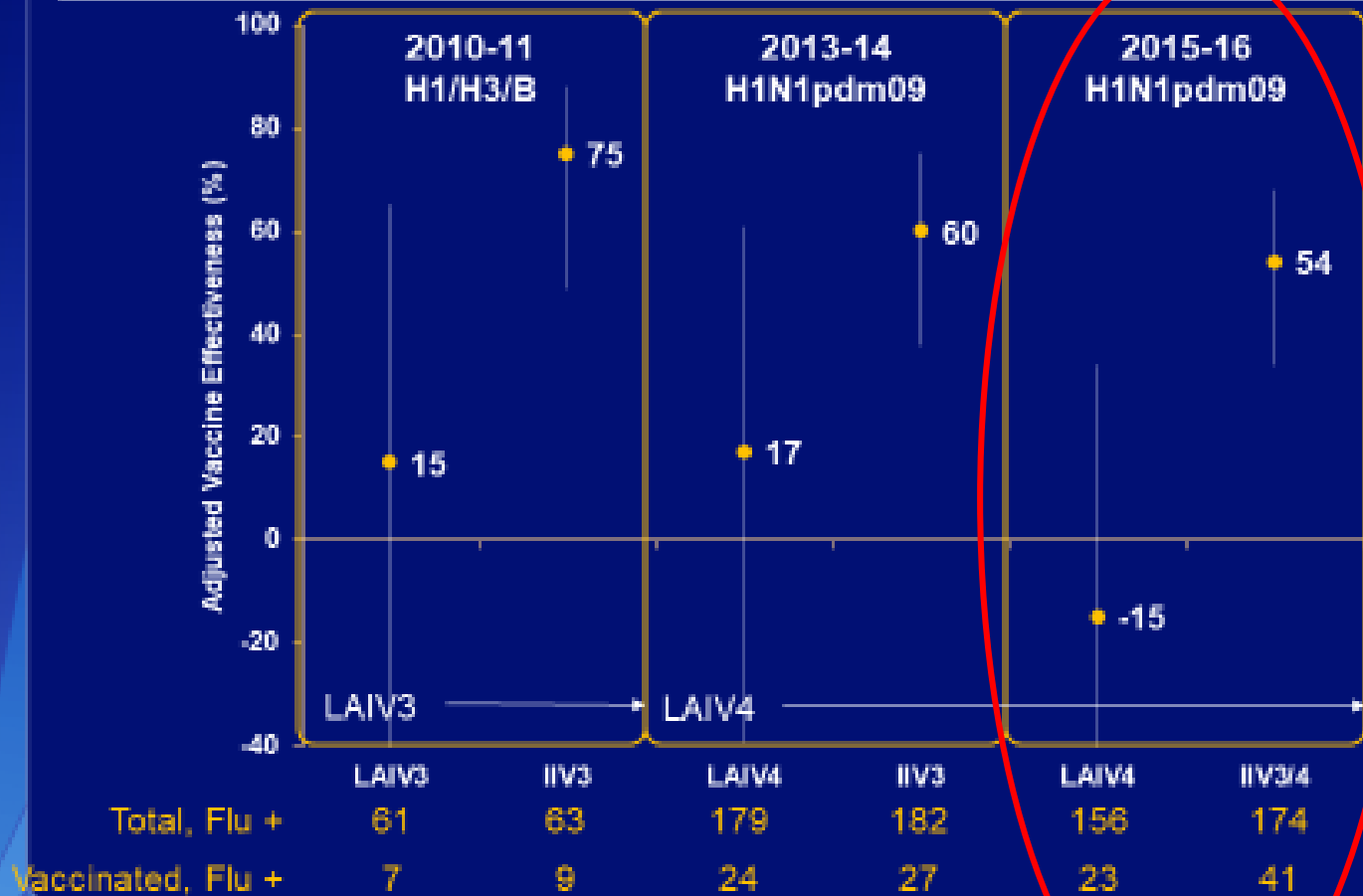
2015-16 Flu season
H1N1pdm09

2016-17 Flu season
H3N2

Feb
2015

June
2016

US Flu VE Network: LAIV and IIV VE age 2-17 yrs A/H1N1pdm09



**2015-16: LAIV
worked less well
against H1N1pdm09
than IIV**

**Other US studies:
Medimmune ICICLE and
DoD**

**Other countries with LAIV
VE: UK, Finland, Canada,
Germany**

US LAIV Policy timeline

ACIP does not recommended
LAIV for 2016-17

2015-16 final season LAIV
and IIV VE shared with
ACIP

ACIP does not recommended
LAIV for 2017-18

Worked on meta-analysis of global studies and IPD
analysis of US studies since 2013-14

Revised methodology to select H1 LAIV virus, human cell
lines, ferret studies LAIV H1 changed to A/Slovenia

2015-16 Flu season
H1N1pdm09

June
2016

2016-17 Flu season
H3N2

June
2017



US LAIV Policy timeline

ACIP does not recommended
LAIV for 2017-18

ACIP recommends LAIV for
2018-19

Meta-analysis of global
estimates; IPD of US data

RCT comparing shedding and Abs for
LAIV with A/Bolivia and A/Slovenia



2016-17 Flu season
H3N2

June
2017

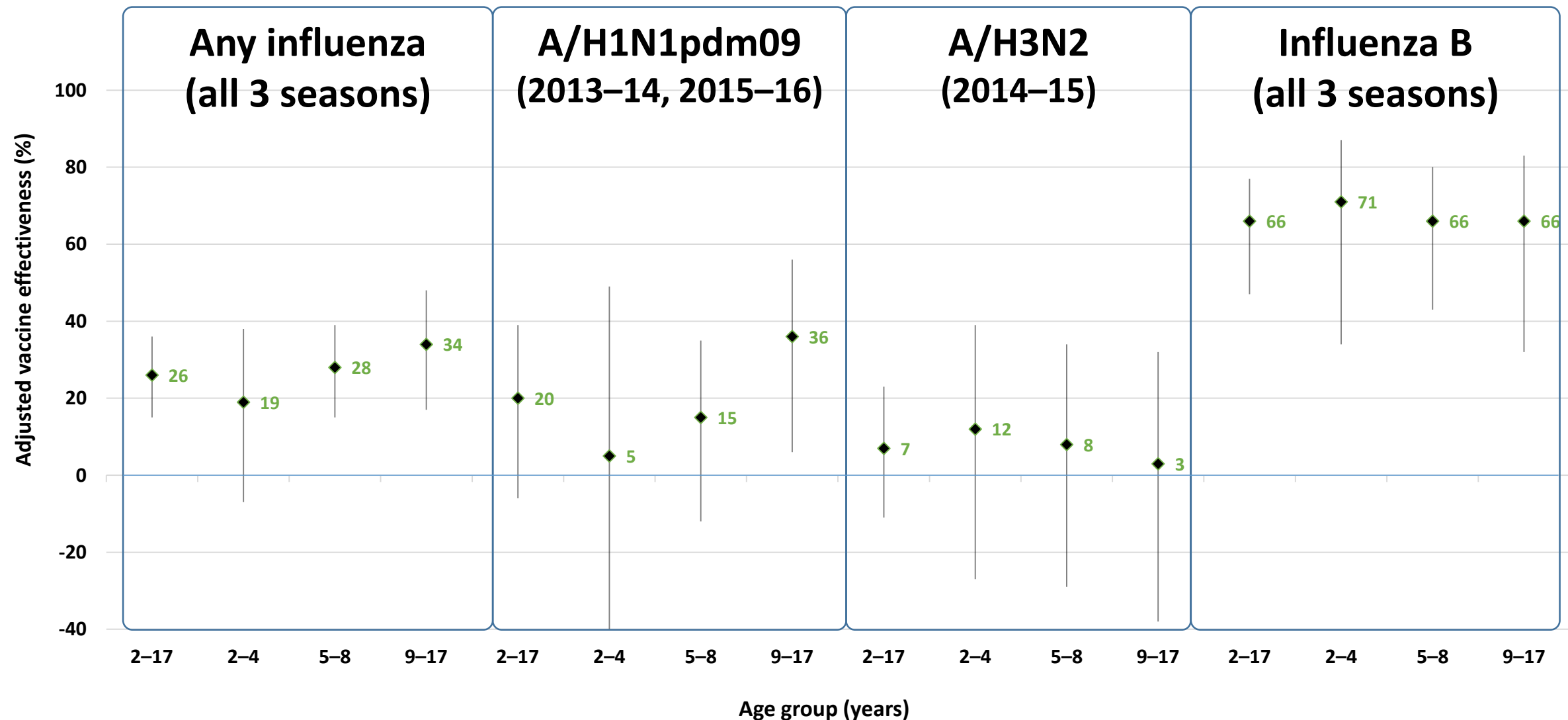
2017-18 Flu season
H3N2

Feb
2018

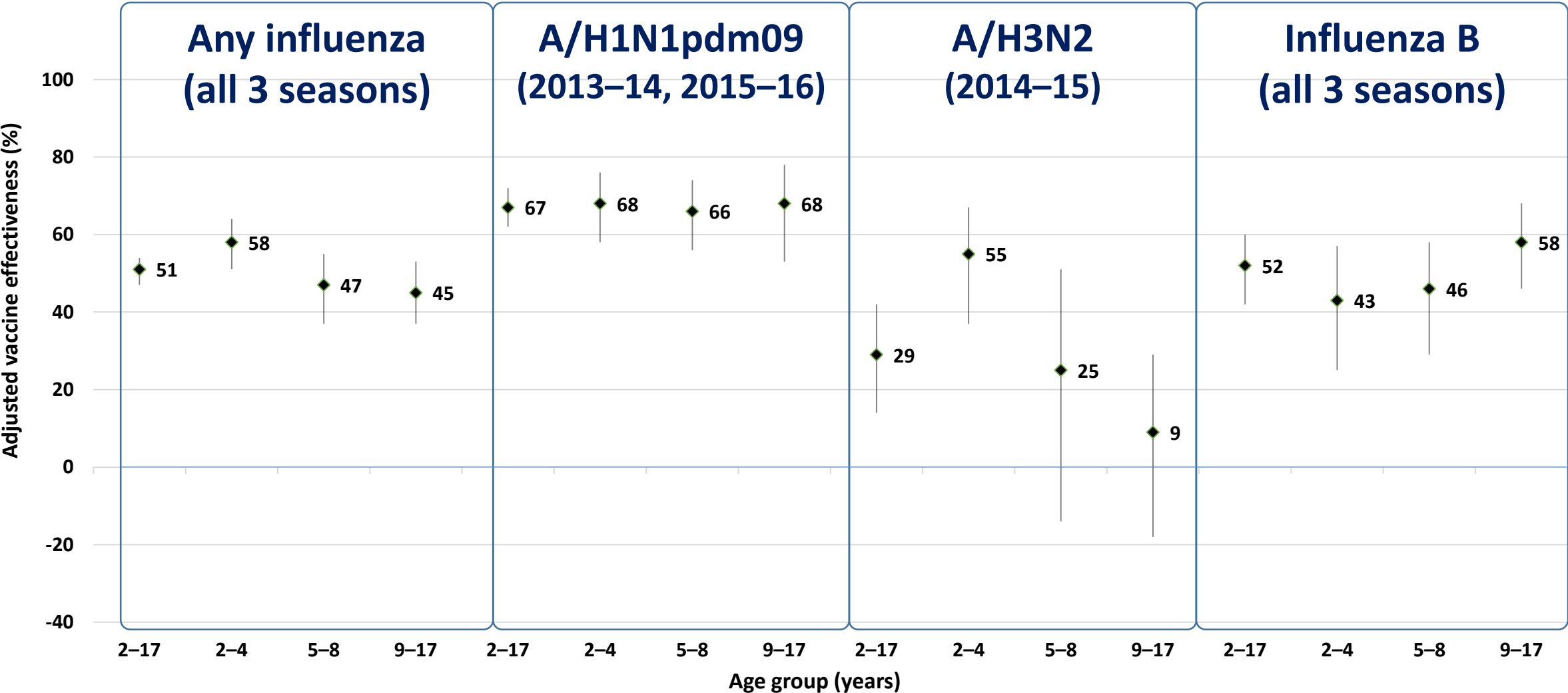
Review of LAIV Effectiveness data, 2010-11 through 2016-17

- Combined individual patient-level analysis of U.S. studies
 - 5 studies and three seasons with LAIV4 (2013-14 through 2015-16)
 - Greater power for age group analyses
 - More precise estimates through pooling of data across multiple studies
 - Evaluation of effect of prior vaccination
- Systematic review and meta-analysis
 - Global studies from 2010-11 season forward
 - Evaluation of quality of individual studies (risk of bias; problems related to small sample size); for observational studies: ROBINS-I and sparse data bias
 - Summary VE results and exploration of heterogeneity

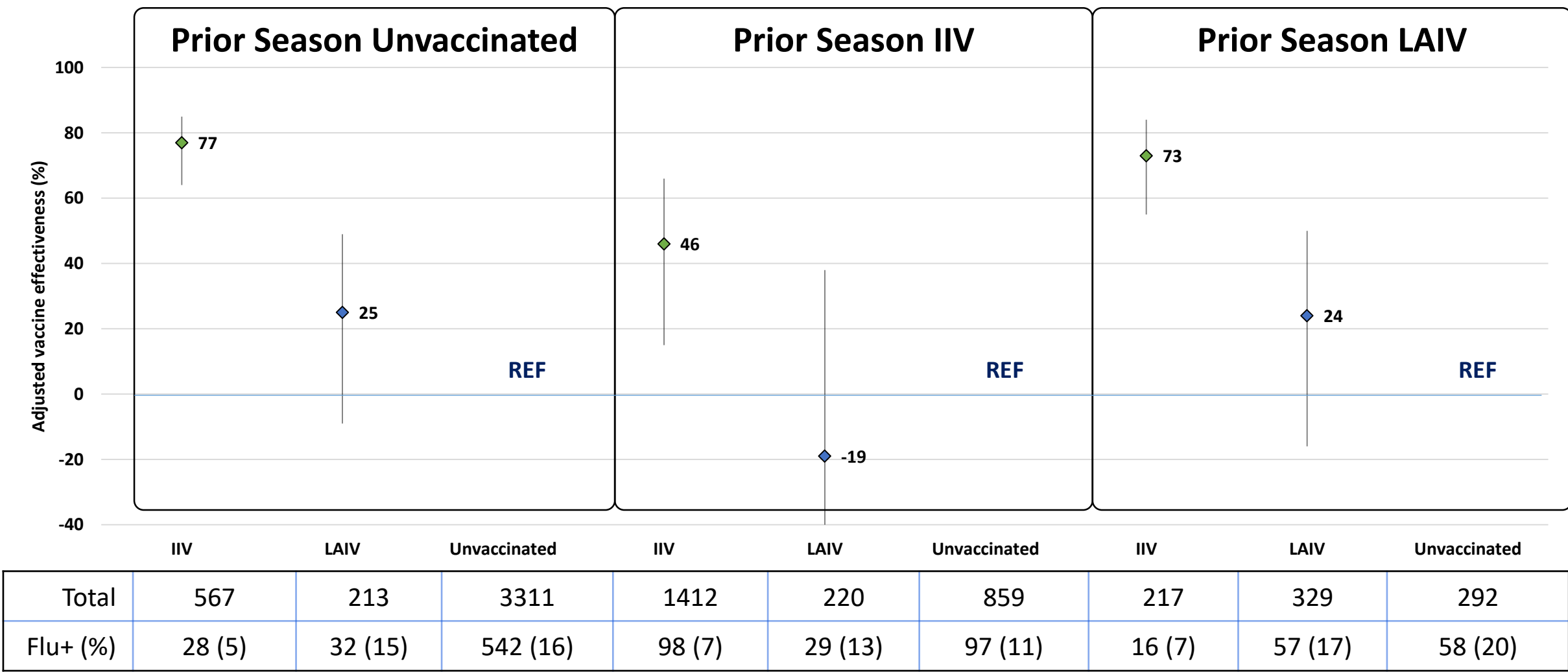
Adjusted VE of LAIV by influenza (sub)type and age group—Combined US-IPD analysis



Adjusted VE of IIV by influenza (sub)type and age group—Combined US-IPD analysis

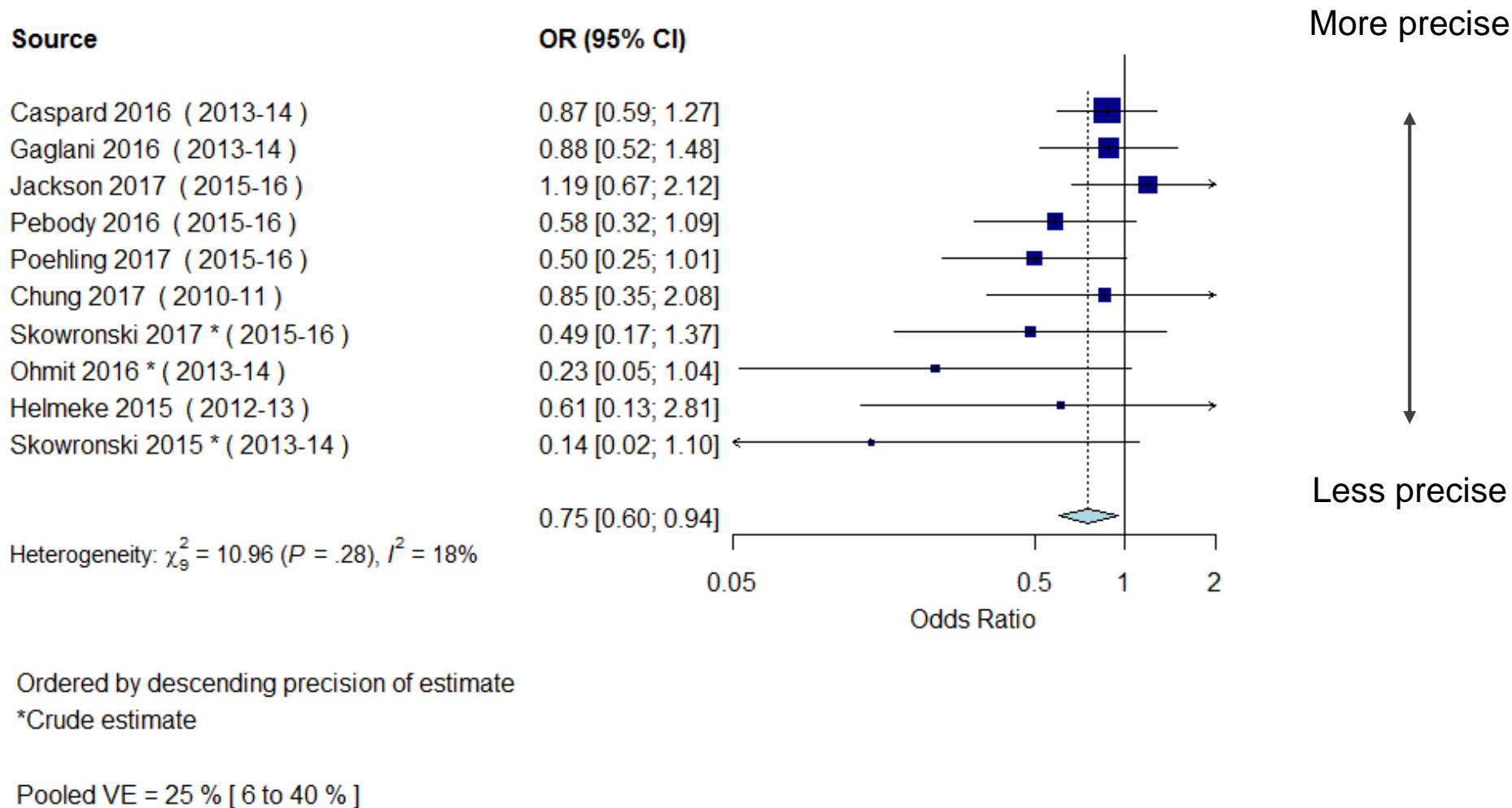


Effect on prior vaccination on VE against A/H1N1pdm09, 2013–14 and 2015–16 seasons—Combined US-IPD analysis



Systematic Review and Meta-analysis of Global studies: Odds of influenza A(H1N1)pdm09 virus infection among children receiving LAIV compared to unvaccinated children, age 2-17 yr, by precision (n=10)

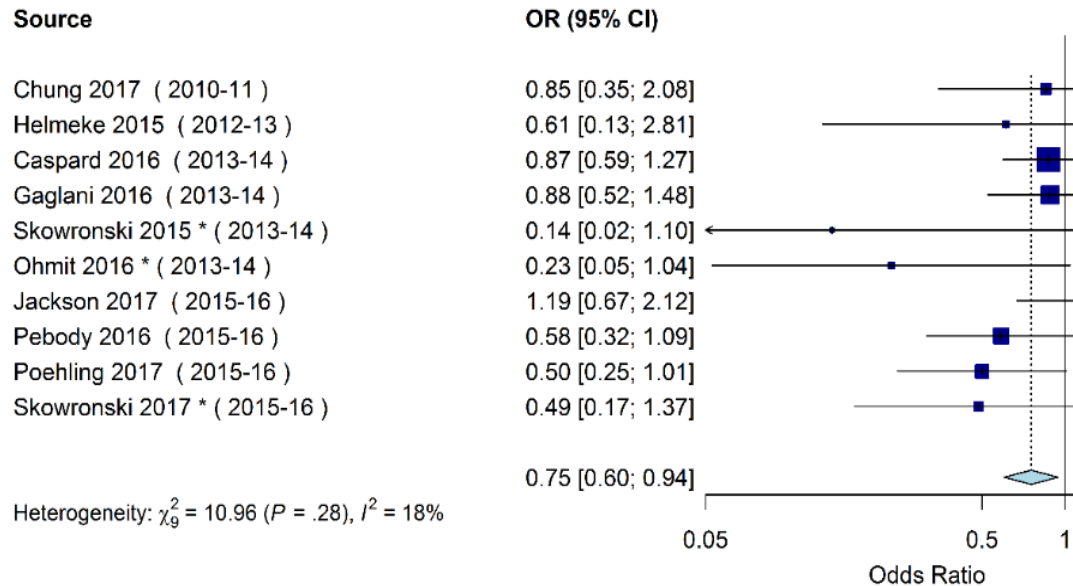
Pooled VE
LAIV vs.
unvaccinated
25% (6 to 40)



Sensitivity Analysis: Inclusion of *Nohynek 2016* influenza A estimate†

Odds of influenza A(H1N1)pdm09 virus infection among children receiving LAIV compared to unvaccinated children, age 2-17 yr

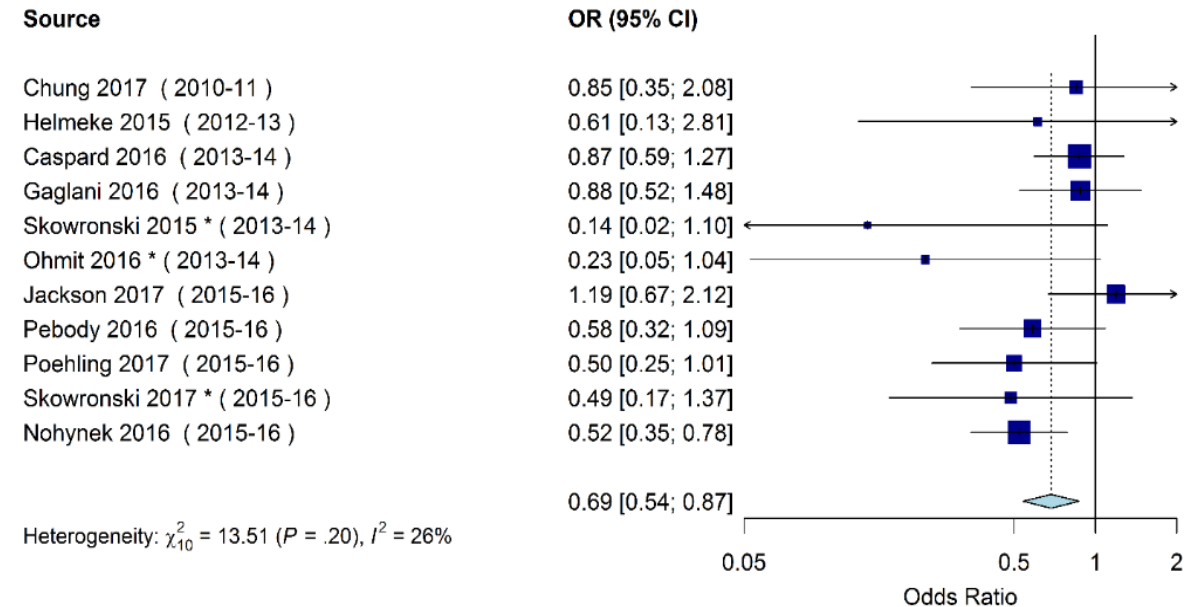
Without Nohynek 2016



Ordered by season
*Crude estimate

**Pooled VE excluding *Nohynek et al*
LAIV vs. unvaccinated:
25% (6 to 40)**

With Nohynek 2016

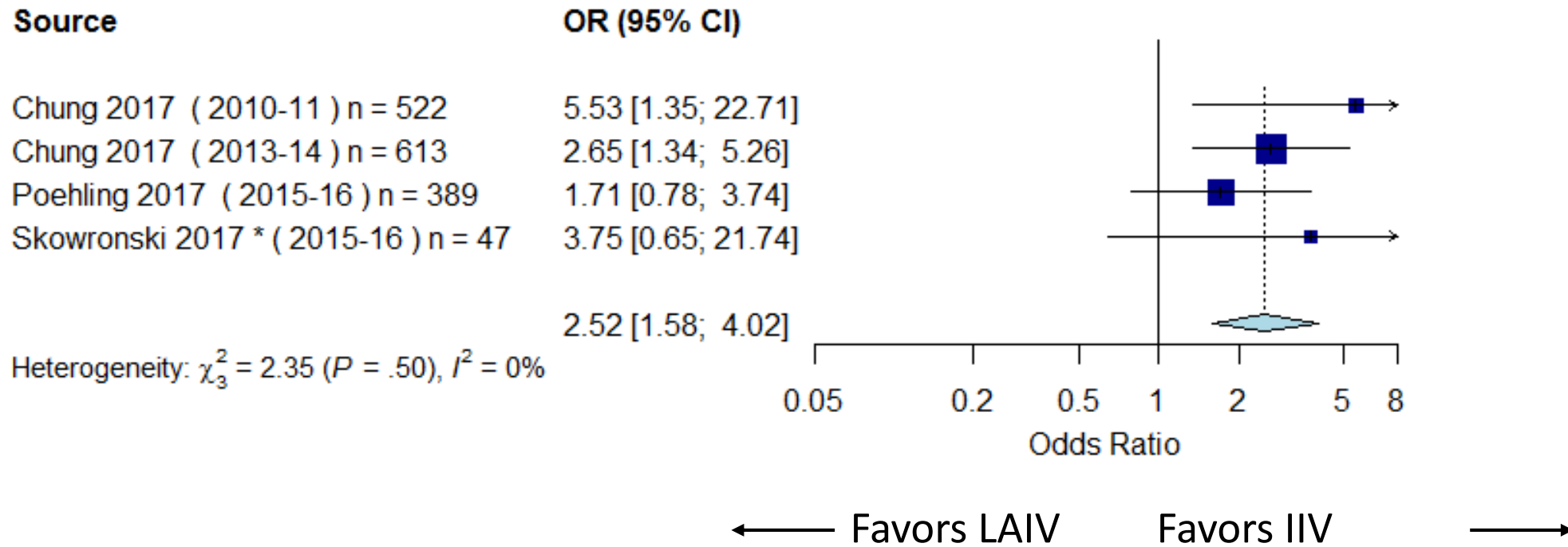


Ordered by season
*Crude estimate

**Pooled VE including *Nohynek et al*
LAIV vs. unvaccinated:
31% (13 to 46)**

†Estimate for Influenza A, presumed predominantly H1N1pdm09; study population includes only 2-year-olds

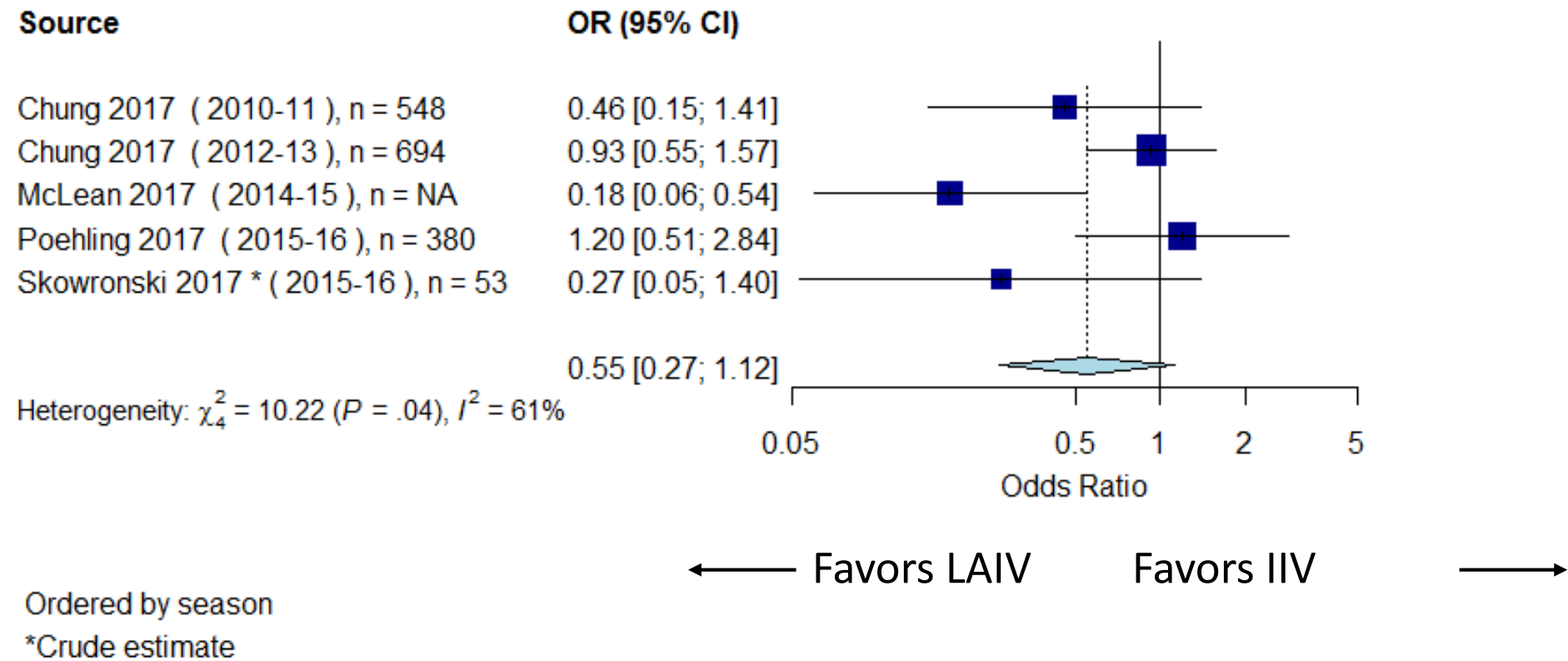
Odds of influenza A(H1N1)pdm09 virus infection among children receiving LAIV compared to children receiving IIV (relative effectiveness), age 2-17 yr (n=4)



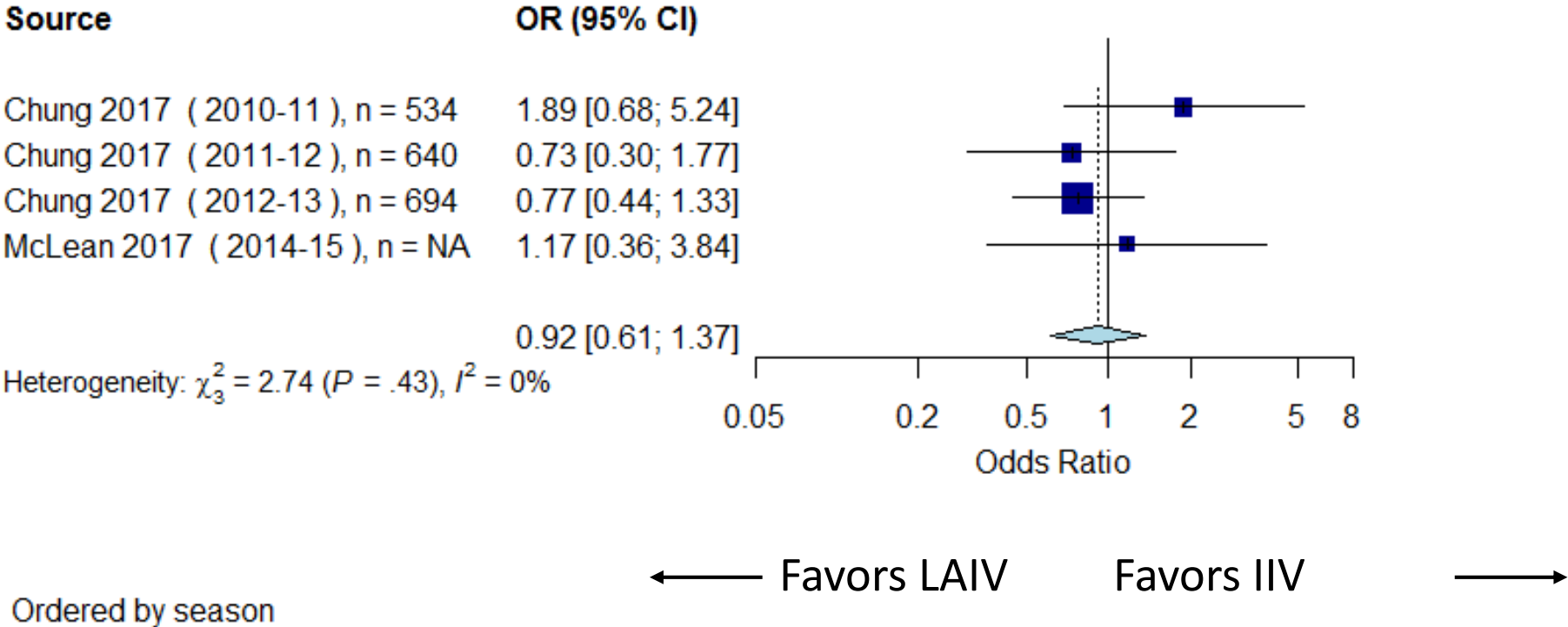
Ordered by season

*Crude estimate

Odds of influenza B virus infection among children receiving LAIV compared to children receiving IIV (relative effectiveness), age 2-17 yr (n=5)



Odds of influenza A(H3N2) virus infection among children receiving LAIV compared to children receiving IIV (relative effectiveness), age 2-17 yr (n=4)



Medimmune presentations at ACIP:

- A/Slovenia/H1N1pdm-like virus performed better in human cell lines and ferret studies than A/CA or A/Bolivia
- Better immunogenicity and shedding of A/Slovenia/H1N1pdm-like virus compared to A/Bolivia in RCT in young children

ACIP, Feb 2017 Conclusions:

- Since 2013-14, a plausible root cause of poor effectiveness of LAIV4 against H1N1pdm09 identified
- New LAIV vaccine virus selection processes to be applied going forward
- Encouraging shedding and immunogenicity evidence that problem may be addressed with new H1N1pdm09 virus
 - Caveat: whether this problem is solved will not be known until there is an effectiveness estimate against H1N1pdm09

UK 2017-18

Table: Adjusted influenza vaccine effectiveness (VE) against medically-attended laboratory confirmed influenza by age group and influenza type in 2017/18, UK.

Group	A(H3N2) adjusted VE (95% CI)	A(H1N1)pdm09 adjusted VE (95% CI)	B adjusted VE (95% CI)	All adjusted VE (95% CI)
2-17 year old (LAIV only)	-75.5 (-289.6, 21.0)	90.3 (16.4, 98.9)	60.8 (8.2, 83.3)	26.9 (-32.6, 59.7)

*Sample sizes not reported

[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/726342/Influenza vaccine effectiveness in primary care 2017 2018.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/726342/Influenza_vaccine_effectiveness_in_primary_care_2017_2018.pdf)

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