LAIV vs IIV effectiveness Summary of evidence since 2009

Brendan Flannery

Influenza Division, CDC

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2015-16 Season: Summary of US Data

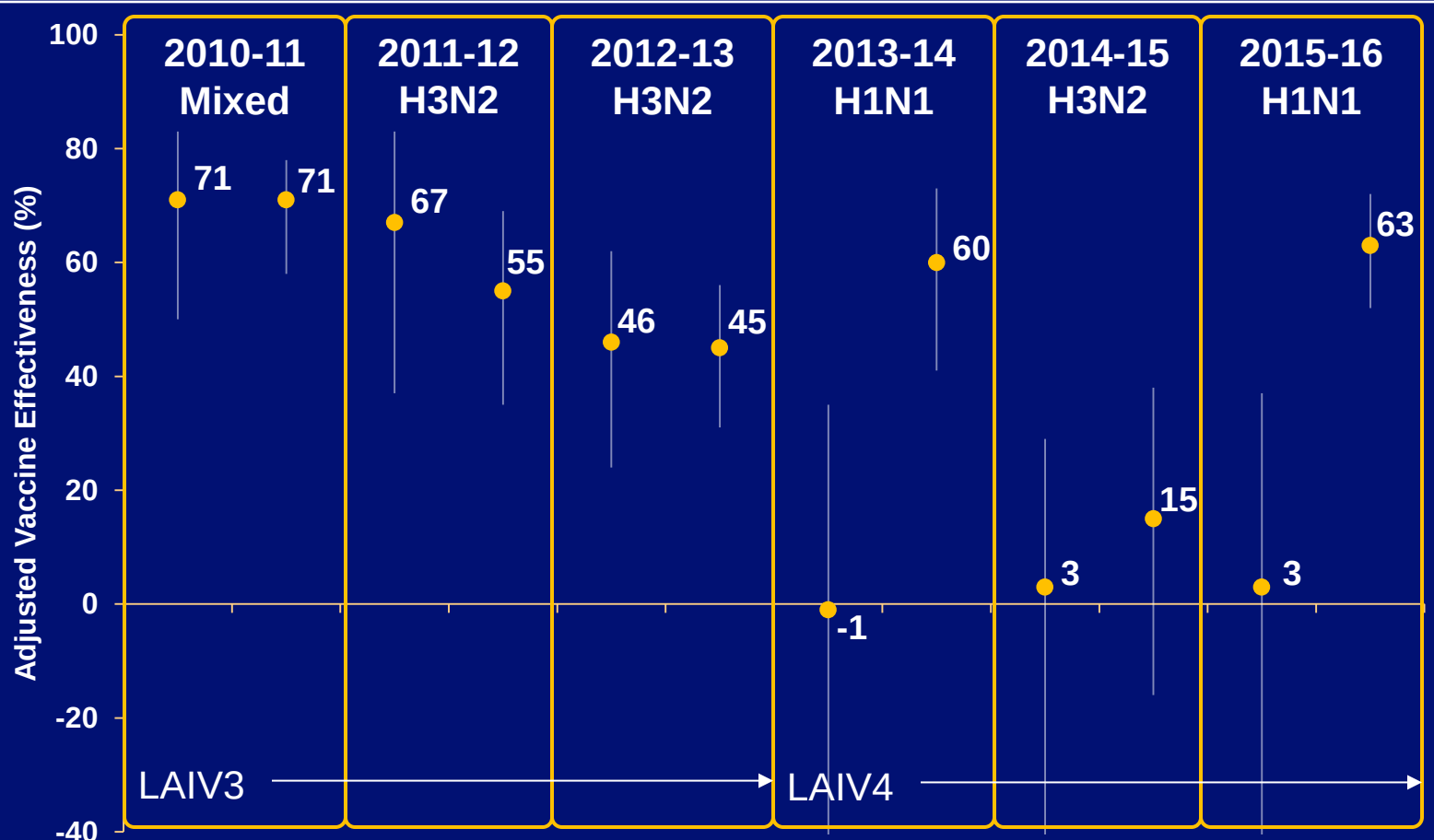
- US Flu VE data indicate no LAIV effectiveness against A/H1N1pdm09; significant VE for IIV
- US DoD test-negative study indicates no LAIV effectiveness against A/H1N1pdm09; significant VE for IIV
- MedImmune test-negative study VE estimate against A/H1N1pdm09 not significant (higher point estimate); significant VE for IIV
- All studies reported higher VE for IIV than LAIV

2015-16 Season: Data from Other Countries

- **UK test-negative VE study**
  - Significant adjusted VE for LAIV against any influenza A or B among children aged 2-17 years (58% [25, 76])
- **National cohort study from Finland**
  - Significant unadjusted VE against flu A (mainly H1N1pdm09) for LAIV in 2-year old children (47% [20, 65]); higher point estimates for IIV (78% [46, 91])
- **No estimate from Canada test-negative study**
- **No estimate from Israel (no LAIV this season)**

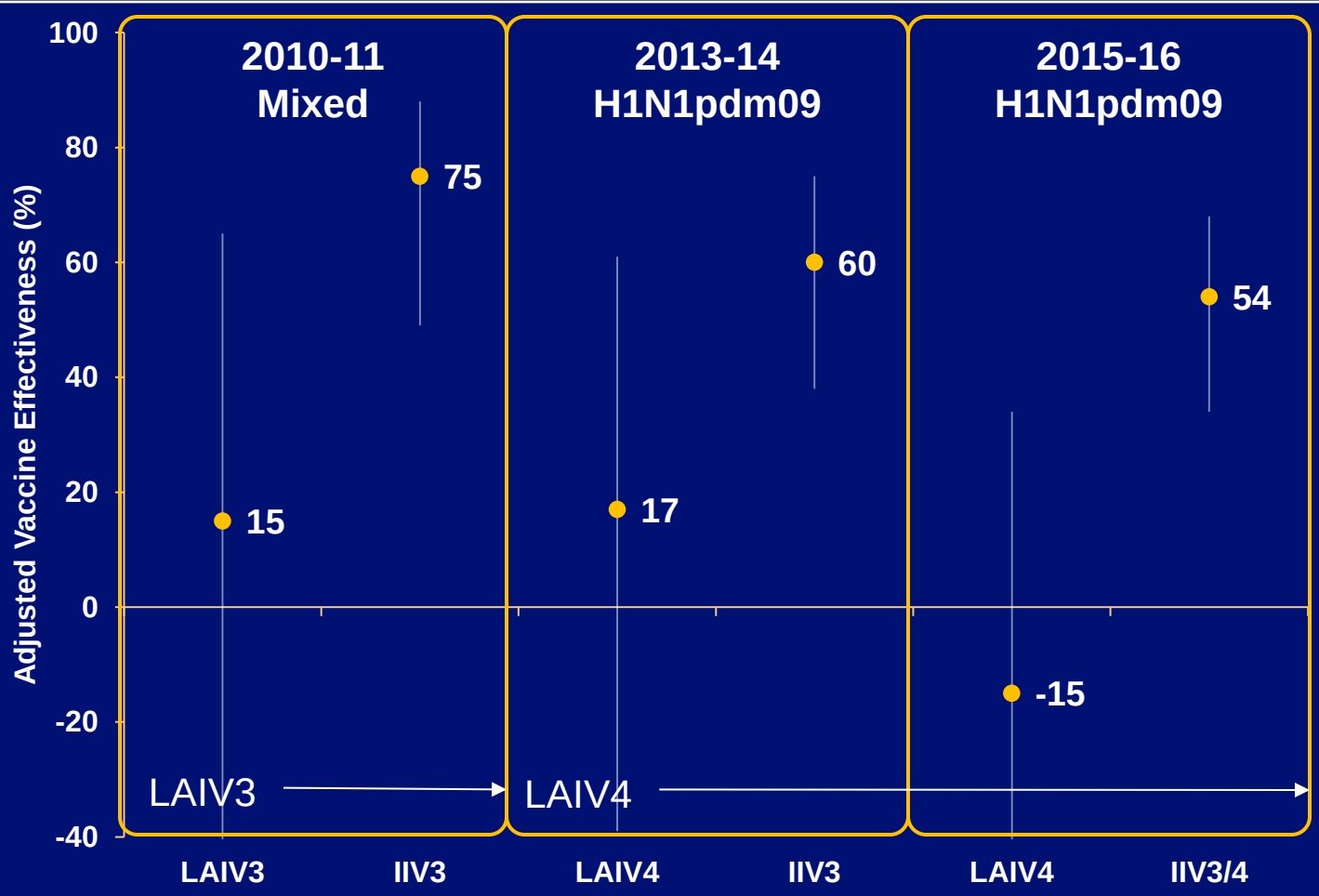
US Flu VE Network 2010-2016

US Flu VE Network: LAIV and IIV VE age 2-17 yrs Any Influenza A or B



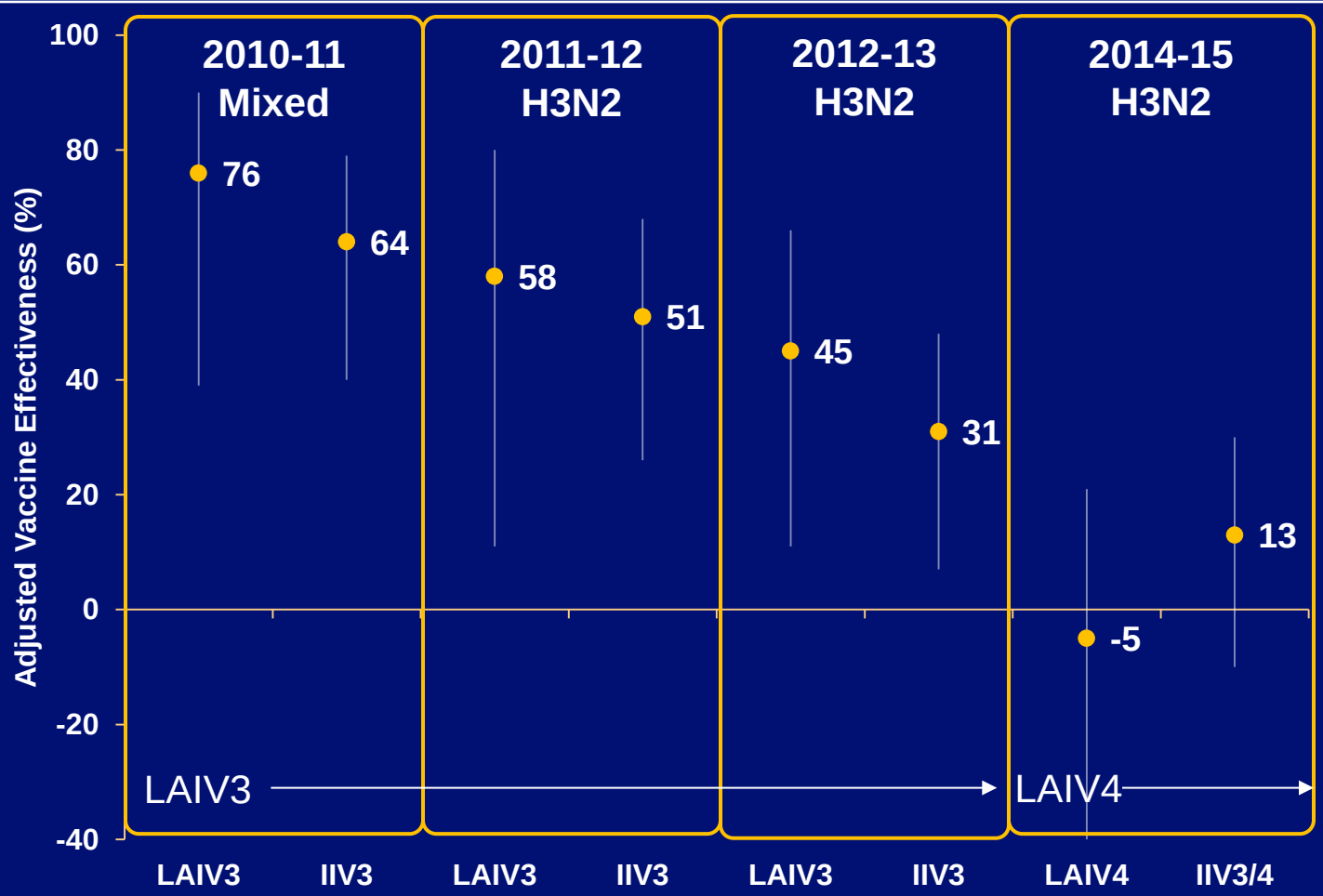
	LAIV3	IIV3	LAIV3	IIV3	LAIV3	IIV3	LAIV4	IIV3	LAIV4	IIV3/4	LAIV4	IIV3/4
Total, Flu +	267	314	225	264	722	859	220	222	588	562	324	367
Vaccinated, Flu +	21	66	12	51	61	198	34	36	106	180	38	81

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



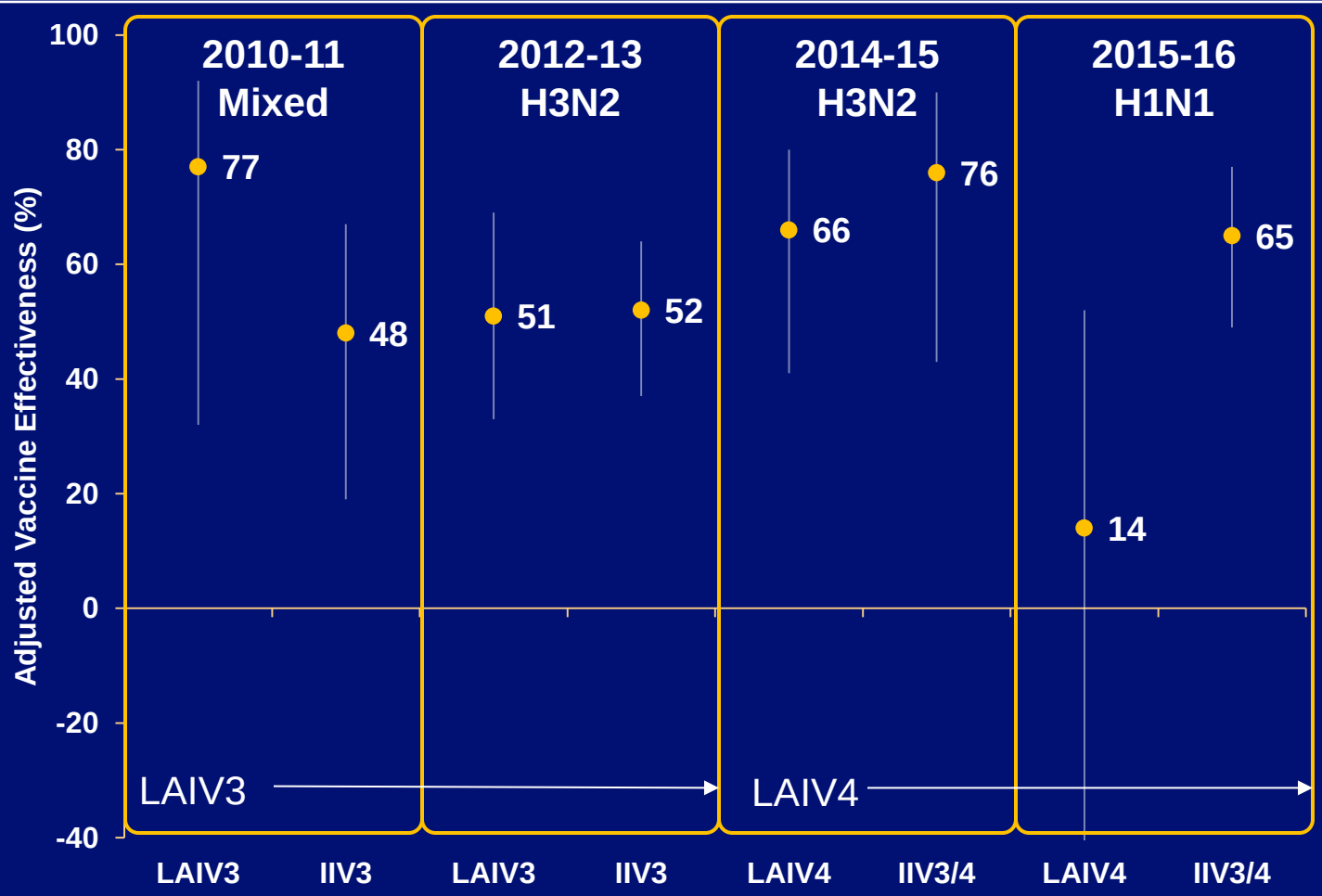
	LAIV3	IIV3	LAIV4	IIV3	LAIV4	IIV3/4
Total, Flu +	61	63	179	182	156	174
Vaccinated, Flu +	7	9	24	27	23	41

US Flu VE Network: LAIV and IIV VE age 2-17 yrs A/H3N2



	LAIV3	IIV3	LAIV3	IIV3	LAIV3	IIV3	LAIV4	IIV3/4
Total, Flu +	91	105	155	187	290	362	490	554
Vaccinated, Flu +	8	20	10	42	27	99	99	163

US Flu VE Network: LAIV and IIV VE age 2-17 yrs Influenza B (both lineages)



	LAIV3	IIV3	LAIV3	IIV3	LAIV4	IIV3/4	LAIV4	IIV3/4
Total, Flu +	113	145	408	474	98	108	149	171
Vaccinated, Flu +	5	37	30	96	7	17	18	40

2013-14 data from observational studies in the US (LAIV4) and studies outside US (LAIV3)

Evidence for children from observational studies in US, 2013-14 season

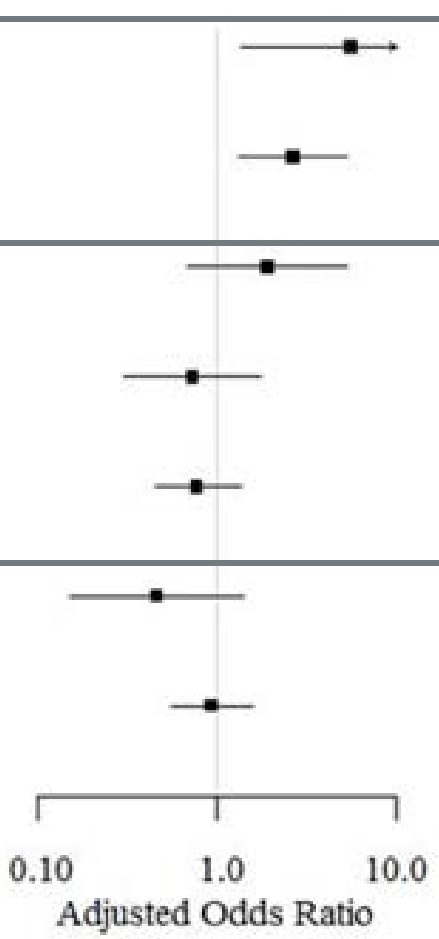
- **3 test-negative VE studies in US during 2013-14**
  - US Flu VE (Gaglani 2016): LAIV4 VE H1N1pdm: 17% (-39 to 51)
  - ICICLE (Caspard 2016): LAIV4 VE H1N1pdm: 13% (-5 to 51)
  - DoD (unpublished): LAIV4 VE H1N1pdm: not significant
  - All reported significant VE for IIV3 against H1N1pdm
- **Basis for change of LAIV H1N1pdm09 strain**
  - 2015-16 first season with updated H1N1pdm09 construct
- **1 US household cohort study during 2013-14**
  - HIVE, MI, ages 2-8 years (Ohmit 2016):

    LAIV4 VE 82% (-65 to 98); IIV3 VE 65% (-3 to 88)

    Only 1 LAIV case

Relative effectiveness of LAIV to IIV, aged 2-17 yrs over 4 influenza seasons, US Flu VE Network

Influenza Type/ Subtype	Influenza Season	Vaccine	Total	No. (%) Positive	aOR
A/H1N1pdm09	2010-2011	LAIV	102	7 (9)	5.53
		IIV	420	9 (2)	REF
	2013-2014	LAIV	154	24 (16)	2.65
		IIV	459	27 (6)	REF
A/H3N2	2010-2011	LAIV	103	8 (8)	1.89
		IIV	431	20 (5)	REF
	2011-2012	LAIV	150	10 (7)	0.73
		IIV	490	42 (9)	REF
	2012-2013	LAIV	171	27 (16)	0.77
		IIV	523	99 (19)	REF
B	2010-2011	LAIV	100	5 (5)	0.46
		IIV	448	37 (8)	REF
	2012-2013	LAIV	174	30 (17)	0.93
		IIV	520	96 (18)	REF



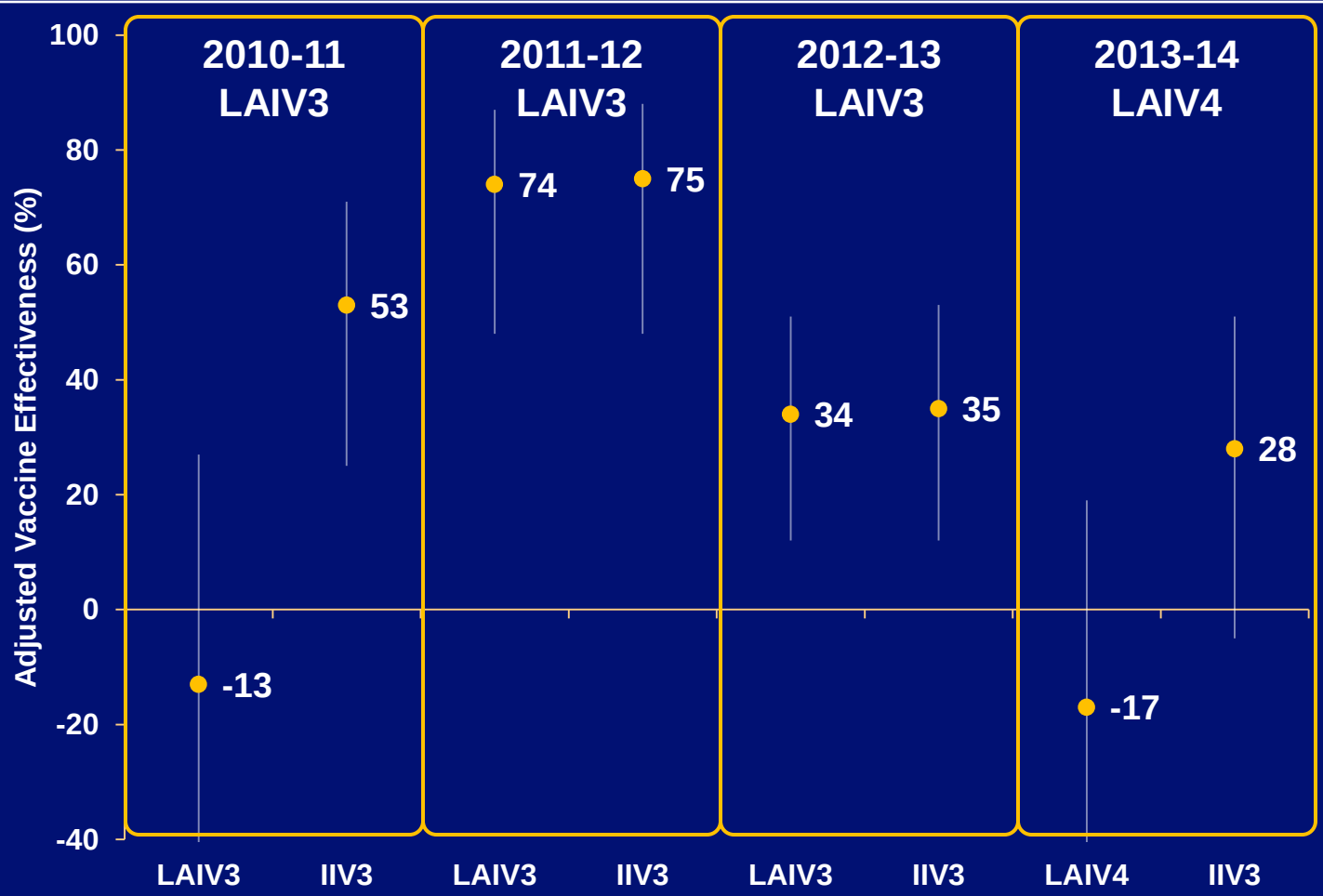
Source: Chung, Pediatrics 2016

Summary of VE against A/H1N1pdm09: studies outside US, 2013-14

- **UK, observational study (Pebody 2014)**
  - Test-negative: VE against A/H1N1pdm09: not significant
  - Ecological: trend of lower flu incidence in LAIV3 pilot areas
- **Canada, observational study (Skowronski 2015)**
  - Test-negative: LAIV3 VE 86% (-11 to 98), not significant (only 1 LAIV case)
- **Canada, cluster randomized trial (Kwong 2014)**
  - Reduced flu incidence in LAIV3 vs IIV3 vaccinated students: HR 0.10, 95% CI 0.01 to 0.84
  - Reduced flu in contacts of LAIV3 vs IIV3 vaccinated students: HR 0.32, CI 0.12 to 0.89

LAIV vs IIV Effectiveness in Adults– US DoD Global Laboratory-based Influenza Surveillance

LAIV and IIV effectiveness against any influenza active military, aged 18+ years, 2010-2014*



Total, Flu +	425	288	116	83	504	332	324	183
Vaccinated, Flu +	307	170	62	29	408	234	181	59

*Eick-Cost 2012; MacIntosh 2013; Eick-Cost 2013; Cost 2014

Summary of serologic and viral shedding data for LAIV H1N1pdm09 virus in children since 2009

- **Limited data on serologic response to A/H1N1pdm09 LAIV vaccine component**
  - Response to A/H1N1pdm LAIV component less than A/H3N2[1]
  - Limited increase in A/H1N1pdm titers observed among children with low pre-vaccine baseline titers[2]
- **A/H1N1pdm virus shedding following LAIV reduced following repeat LAIV[3]**
  - No influence of pre-vaccination serum antibody titer

[1] Mohn, JID 2014; [2]US Flu VE network (unpublished); [3]Ilyushina, JID 2014

Summary of available data for LAIV VE since 2009

- **Preliminary US Flu VE Network data for 2015-16 indicated that quadrivalent LAIV offered no significant protection against influenza A (H1N1)pdm09 in children aged 2-17**
- **Poor VE for quadrivalent LAIV was observed during two preceding flu seasons in children aged 2-17**
  - 2013-14: No significant VE for LAIV4 against A(H1N1)pdm09
  - 2014-15: No significant VE for LAIV4 or IIV3/4 against drifted A(H3N2) viruses
- **During previous seasons, most evidence demonstrated that LAIV3 worked as well as IIV3 against A(H3N2) and B viruses in children aged 2-17**
- **Poor VE for LAIV3/4 against A(H1N1)pdm09 in active military**

Possible reasons for poor performance of quadrivalent LAIV in 2015-16 season

- **Suboptimal performance of the A/Bolivia/559/2013 (H1N1)pdm09 HA vaccine component**
- **Potential interference among viruses in the quadrivalent vaccine [i.e., additional B vaccine component effects viral replication of A(H1N1)pdm09 virus]**
- **Reduced immunogenicity of LAIV as a result of more highly vaccinated population in recent years; compared with populations of earlier studies, in which it is likely that a higher proportion of children were vaccine-naïve**