2015-16 US Influenza Vaccine Effectiveness
Influenza Clinical Investigation for Children (ICICLE) Study

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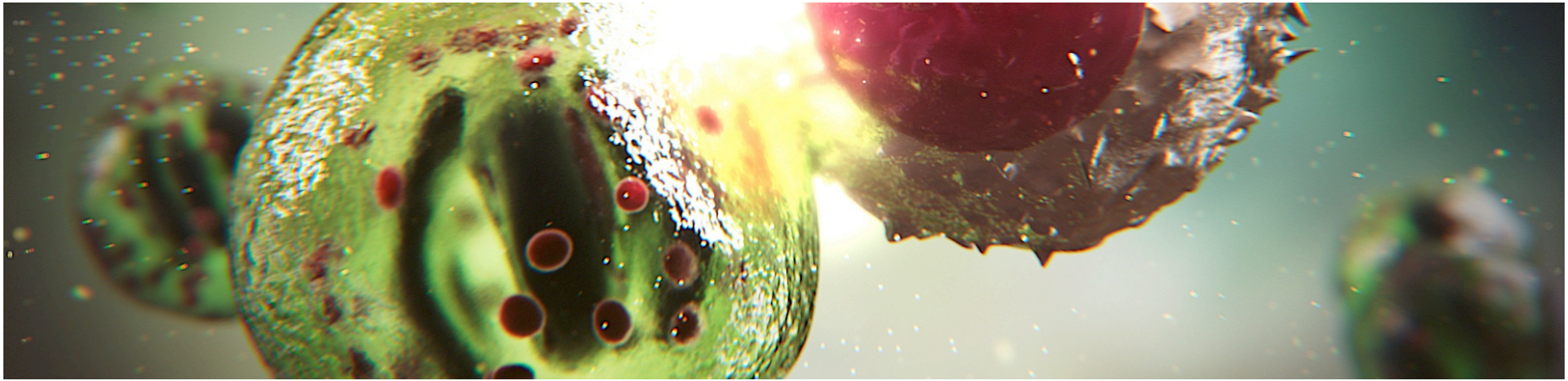


Summary of LAIV and IIV Effectiveness in 2015-16

- ICICLE vaccine effectiveness (VE) study demonstrated significant overall VE for LAIV4 and IIV in US children 2-17 years of age
  - LAIV4: 46% (95% CI: 7, 69) IIV: 65% (95% CI: 48, 76)
- Similar results in 2015-16 in test-negative VE study in the UK and a large cohort study in Finland
- These LAIV4 VE estimates similar to VE observed with IIV in children in recent seasons (e.g. 2011-12 and 2012-13)[1-3]
- No explanation at present for difference compared to CDC LAIV4 VE estimate
  - CDC and ICICLE methods and 2013-14 VE estimates generally similar
  - May relate to limited sample size, statistical power, or limitations of observational study design

1. Ohmit et al, CID 2013. 2. McLean et al, JID, 2014. 3. Flannery B. ACIP presentations. 2014.

ICICLE: Observational, Test-Negative Design Similar to CDC VE Study

- Community-dwelling children 2-17 years of age enrolled at 8 US sites:
  - Marshfield Clinic, Wisconsin (Edward Belongia)*
  - Baylor Scott & White Health, Texas (Manjusha Gaglani)*
  - Vanderbilt University, Tennessee (Marie Griffin)
  - Wake Forest University, North Carolina (Katherine Poehling)
  - Akron Children's Hospital, Ohio (Blaise Congeni)
  - HealthPartners Como Clinic, Minnesota (Poornina Kavathekar)
  - Kaiser Permanente, Oregon (Allison Naleway)
  - University of Florida, Gainesville (Kathleen Ryan)
- Seeking outpatient care for febrile acute respiratory illness with onset <5 days
- Excludes subjects vaccinated <14 days before symptom onset
- Nasal swabs tested by PCR respiratory viral panel
- Sites monitored up to 3 times per season to confirm data accuracy

***Also participate in CDC VE study but at different clinic sites**

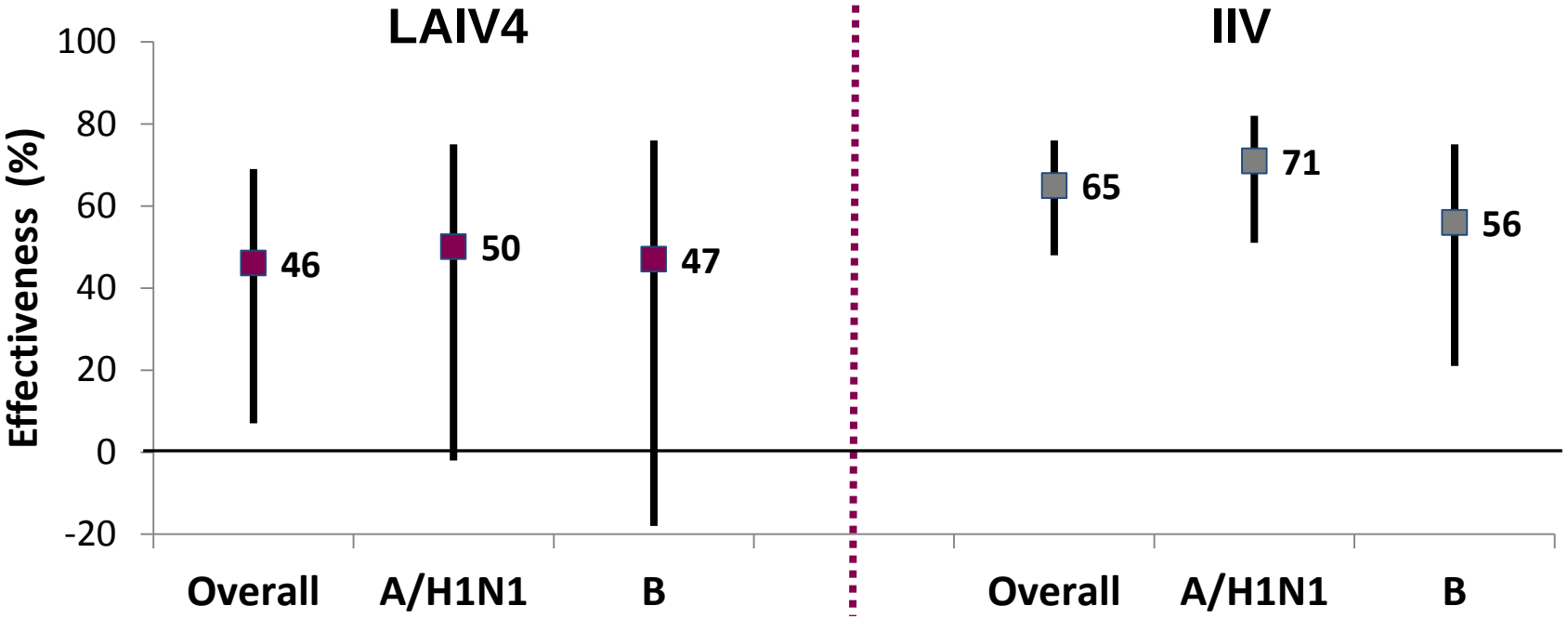
2015-16 ICICLE US Enrollment and Analysis Population

- 1,238 children enrolled from Nov 30, 2015 to Apr 15, 2016
- 226 were excluded from analysis:
  - Enrolled before or after influenza circulation: n=215
  - Vaccination <14 days before illness: n=7
  - Missing documentation of vaccination date and/or type: n=3
  - Lack of signed consent: n=1
- 1,012 subjects retained for analysis:
  - 594 unvaccinated children
  - 101 LAIV4 recipients
  - 317 IIV recipients (202 IIV4, 100 IIV3, 15 unknown)

2015-16 ICICLE Population Characteristics by Vaccine Group

	No Vaccination (n=594)	LAIV4 (n=101)	IIV (n=317)
2 to 4 years 5 to 8 years 9 to 17 years	28% 36% 36%	33% 47% 20%	36% 36% 28%
Privately insured	45%	56%	53%
Chronic condition	16%	6%	26%
Prior vaccination in 2014-15	32%	73%	77%

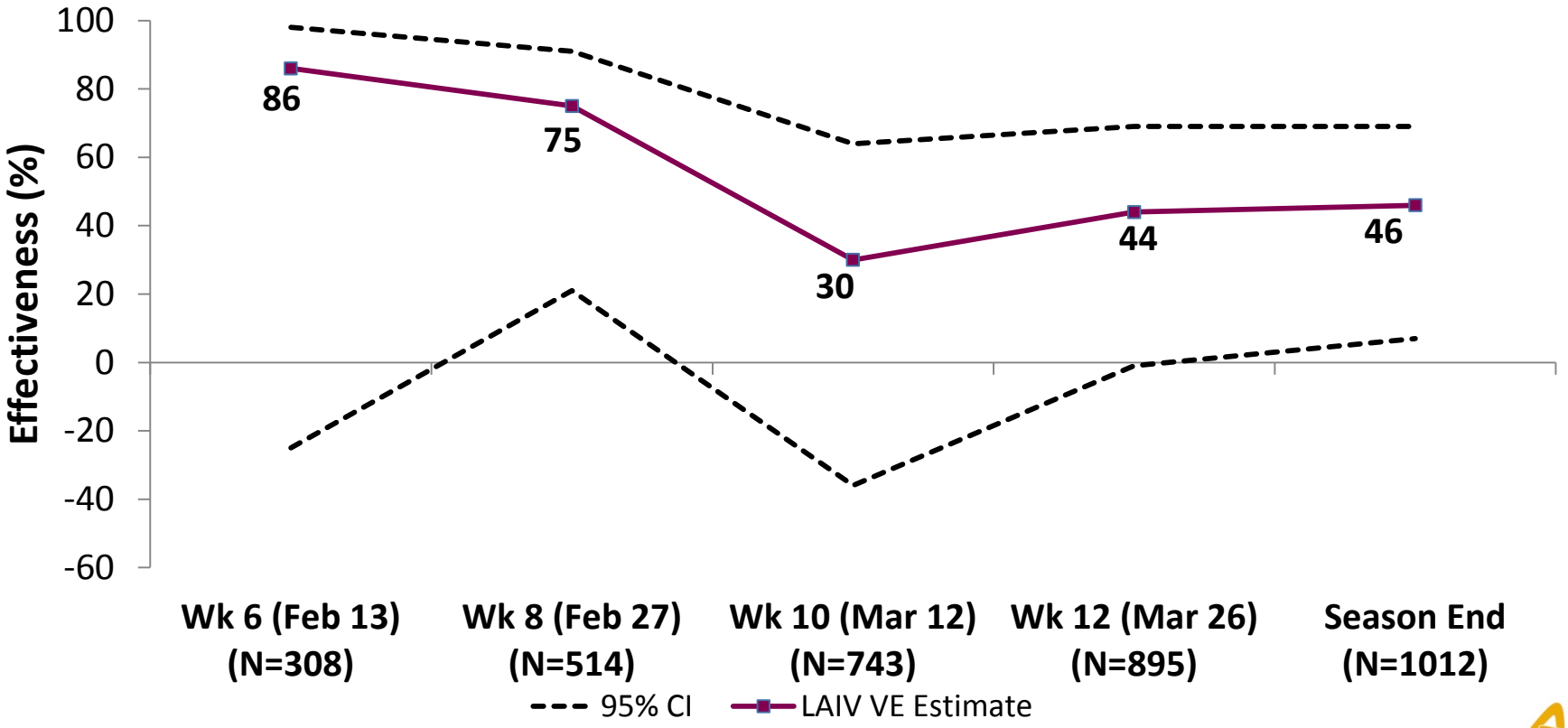
ICICLE: 2015-16 Adjusted Estimates of Effectiveness



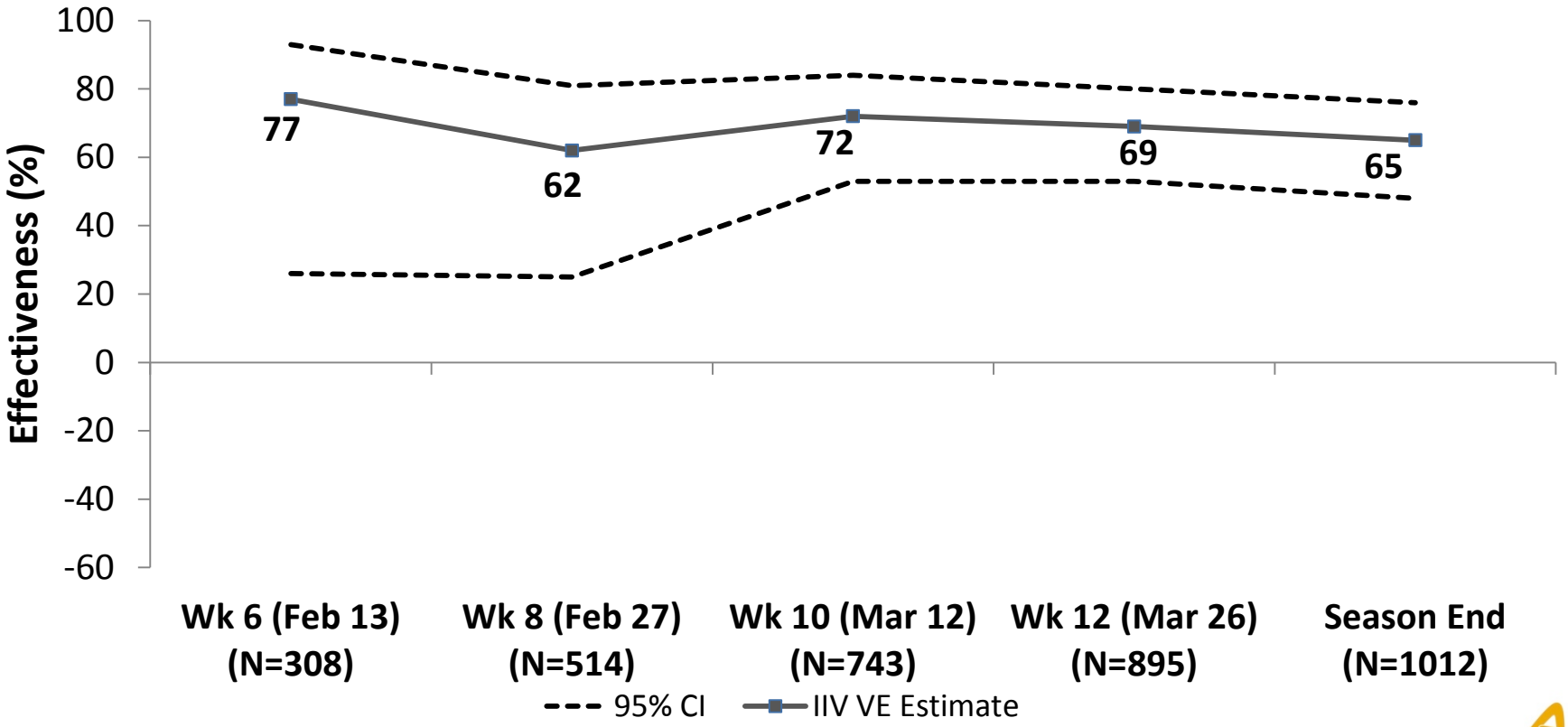
- Results similar for 1) those fully vaccinated, 2) excluding those negative for any respiratory virus, and 3) excluding those with high-risk conditions

VE adjusted on site, age group, visit date, outpatient visits in past 6 months, health insurance, and sex
CI's truncated at -20 to enable graphical display

ICICLE: Overall VE for LAIV4 by Calendar Time



ICICLE: Overall VE for IIV by Calendar Time



2015-2016 VE Study by Public Health England

- Test-negative VE study in UK children 2-17 years of age (N=279)
- Third year of UK vaccination program
  - LAIV4 used in children without contraindications
  - Vaccine uptake of ~40% achieved in young children
- Estimate of overall LAIV4 VE: 57.6% (25.1, 76)

Public Health England statement, June 22, 2016
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/530756/Influenza_vaccine_effectiveness_in_primary_care_in_children.pdf

2015-16 VE Study by Finland National Institute for Health and Welfare

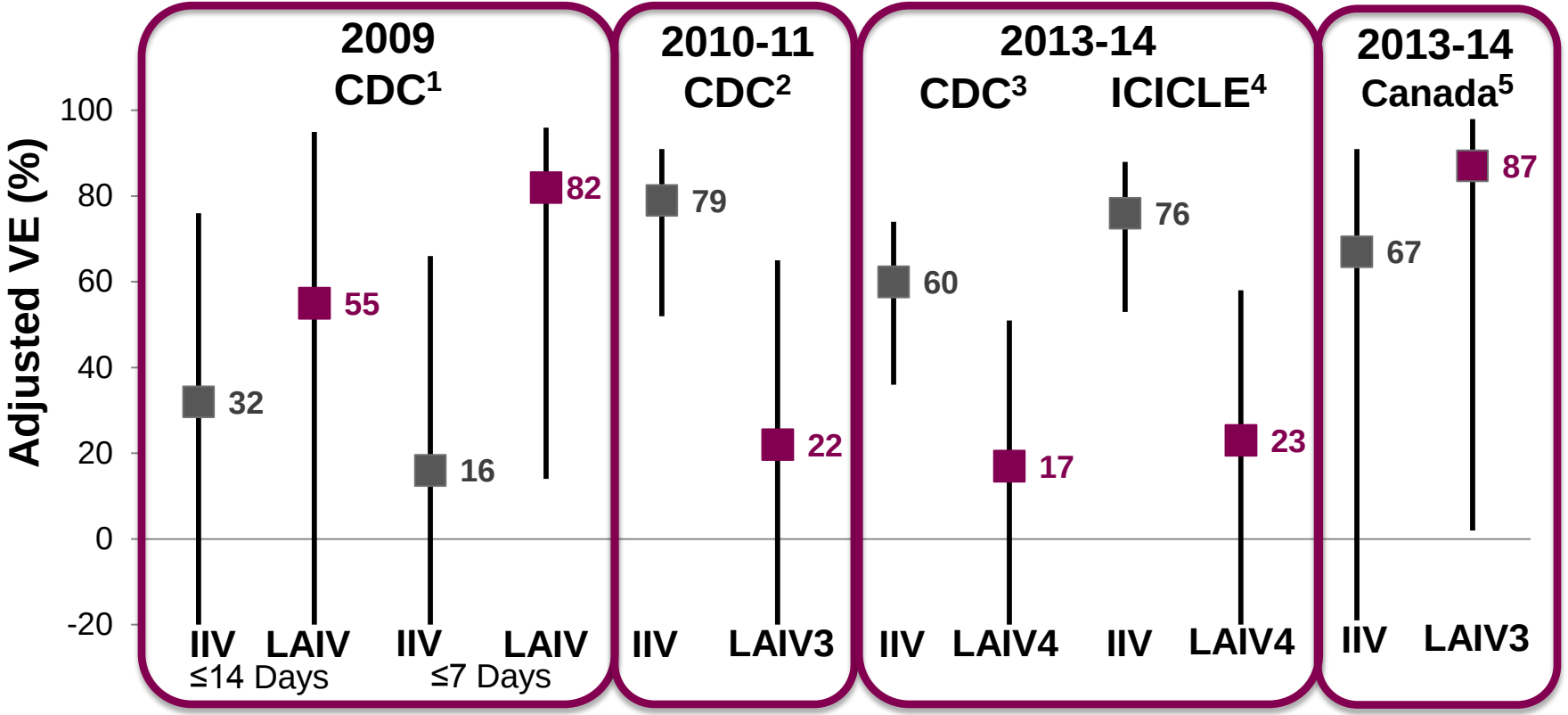
- Cohort VE study in Finland of 58,857 children 24-35 months of age
  - Predominant A strains were H1N1

Finland Cohort Study	Unvaccinated N=46,119	LAIV4 N=8,323	IIV N=4,415	Unadjusted VE LAIV4 (95% CI)	Unadjusted VE IIV (95% CI)
Medically-attended lab-confirmed influenza	321	30	11	46.2 (22, 63)	59.7 (27, 78)
Type A	270	25	5	46.7 (20, 65)	77.7 (46, 91)
Type B	53	6	6	35 (-56, 73)	-20.2 (-179, 48)

Nohynek et al., Nordic Vaccine Meeting, April 2016. Confirmed by personal communication June 21, 2016.

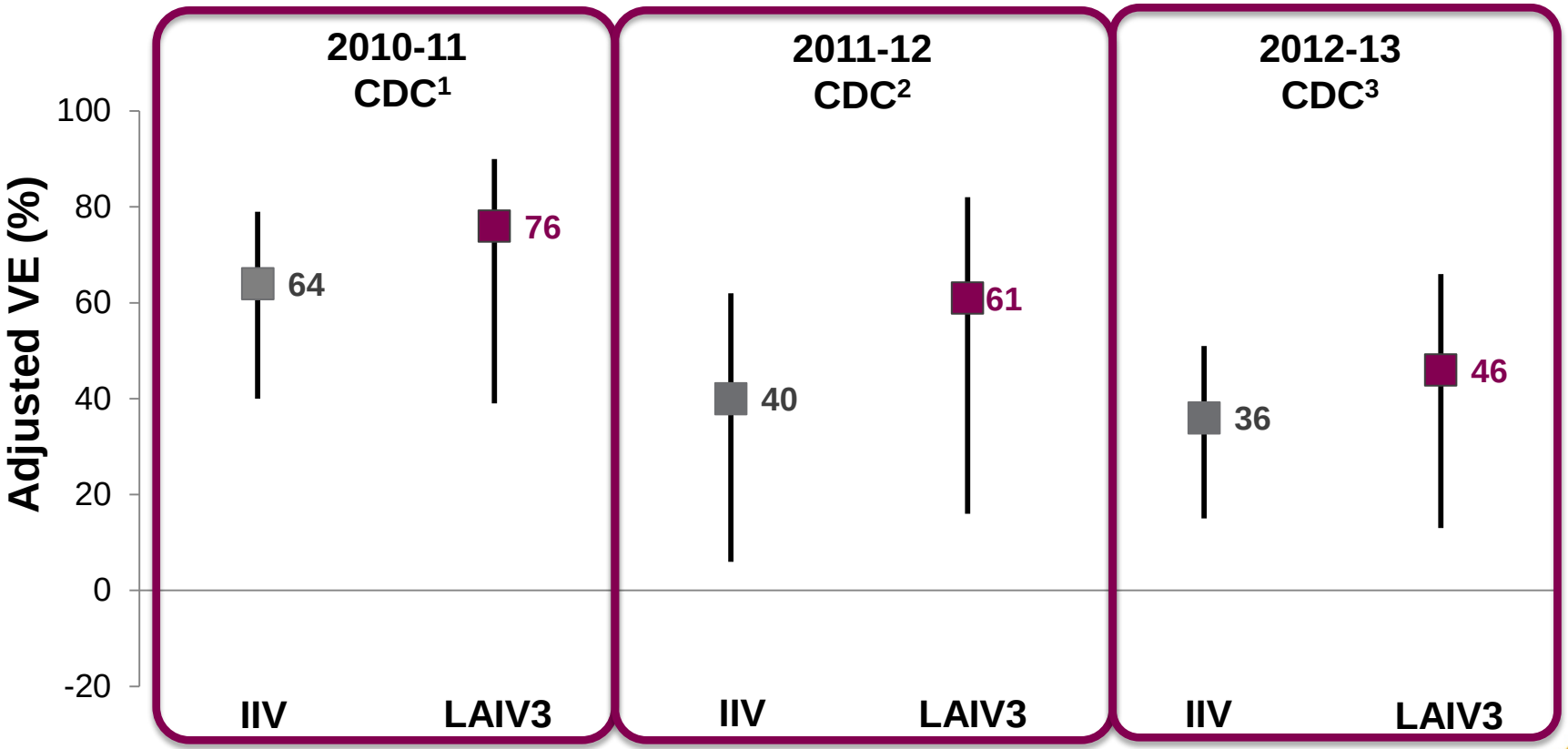
2015-2016 Estimates of Overall Effectiveness of LAIV4

2009-2014 VE of IIV and LAIV Against H1N1pdm09 in Children



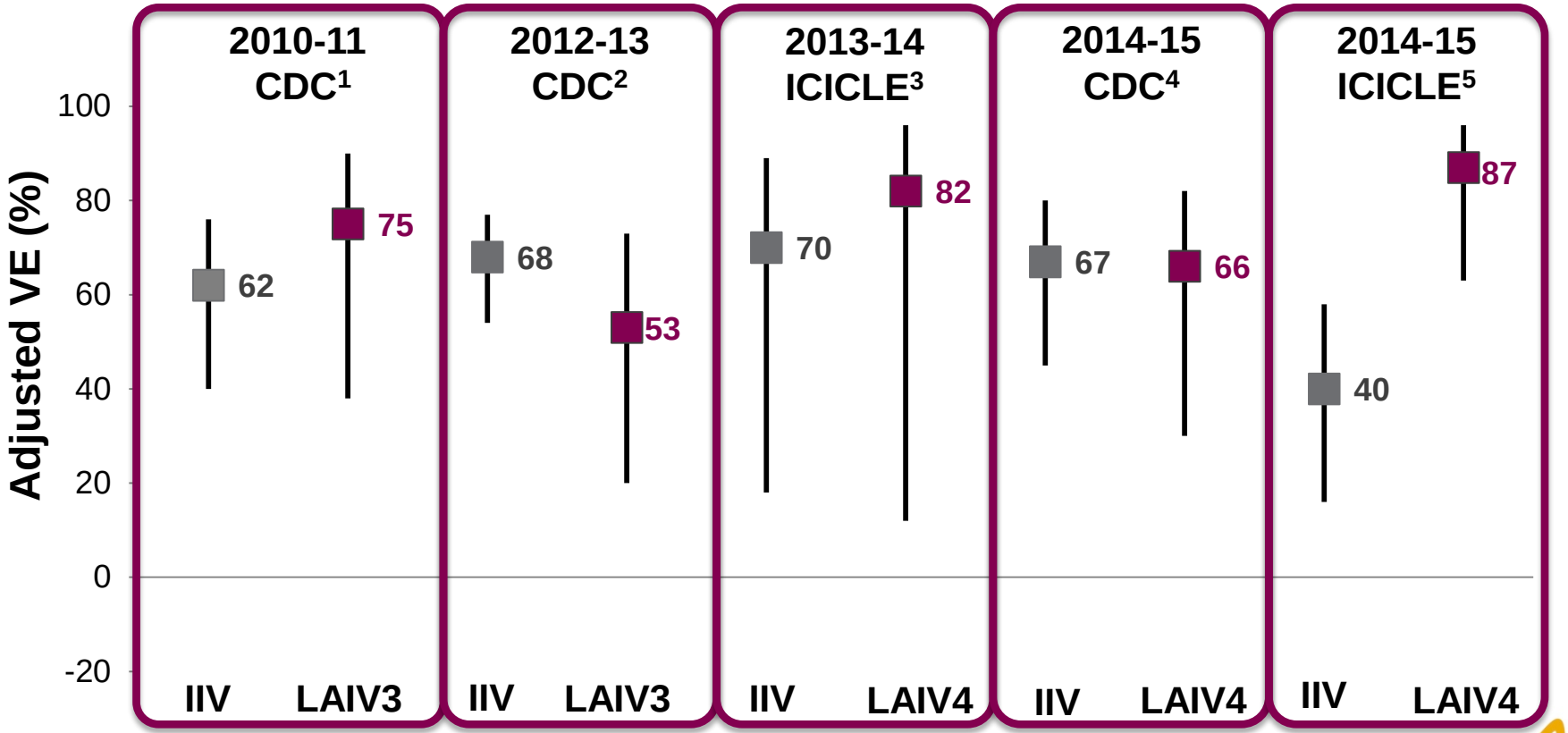
1. LAIV data for children 2-9 years of age and IIV data for children 6mo-9 years of age from Griffin, 2011. 2. Data for children 2-8 years of age from CDC personal communication; 3. Data for fully vaccinated children 2-17 years from Gaglani et al, JID, 2016. 4. Data for fully vaccinated 2-17 yo from Caspard et al, Vaccine, 2016. 5. Skowronski et al, JID, 2015. (Unadjusted VE for 2-19 years in BC, Alberta, Quebec). CI's truncated at -20 to enable graphical display.

2010-2013 VE of IIV and LAIV Against Matched H3N2 in Children



1. Data for children 2-8 years of age from CDC ACIP presentation; 2. Data for children 2-8 years from Ohmit et al, CID 2013; Data for overall VE, as type/subtype-specific VE not available and H3N2 was predominant in 2011-12 (73% of study cases); H1N1pdm09 and B also circulated. 3. Data for children 2-17 years from McLean et al, JID, 2015.

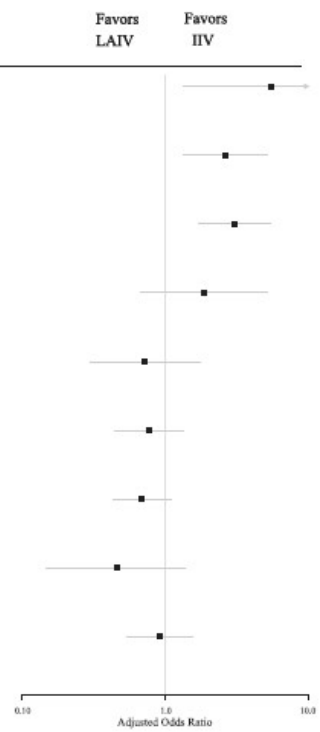
2010-2015 VE of IIV and LAIV Against Influenza B in Children



1. Data for children 2-8 years of age from CDC ACIP presentation; 2. Data for children 2-17 years from McLean et al, JID, 2015. 3. Data for children 2-17 years from Caspard et al, Vaccine, 2016. 4. Flannery B. ACIP presentation. 5. Data on file, manuscript pending publication.

CDC Evaluation of Seasonal Effectiveness of LAIV and IIV in Children 2-17 Years of Age

Influenza Type/ Subtype	Influenza Season	Vaccine Type	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
	Combined*	LAIV	256	31 (12)	3.08
		IIV	879	36 (4)	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
	Combined*	LAIV	321	37 (12)	0.69
		IIV	1013	141 (14)	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



Chung et al, Pediatrics, 2015.

Limitations of Observational Test-Negative VE Estimates

- Potential for bias due to observational study design
- VE estimates can be imprecise, vulnerable to random effects
- Multiple assumptions must be met to ensure study validity
  1. Subjects must be randomly drawn from population of those seeking care
  2. Among those with similar care-seeking behavior, non-influenza illness must be the same among those vaccinated and not vaccinated
  3. Vaccine effectiveness does not vary by health-seeking behavior

Jackson et al., *Vaccine*. 2013.

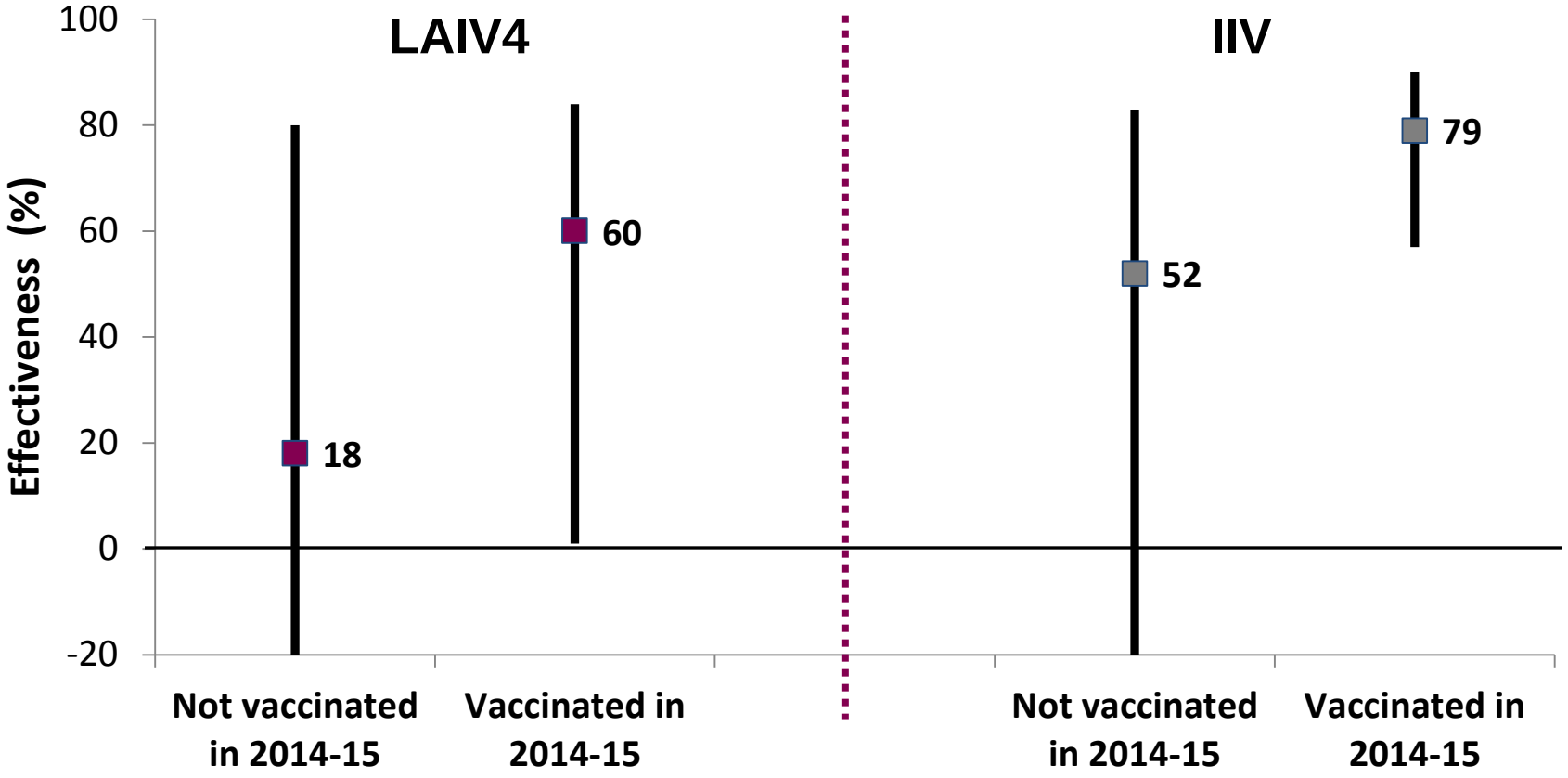
Conclusions

- Three studies demonstrated similar, statistically significant overall VE of LAIV4 in 2015-16 in children 2-17 years of age of 46% to 58%
  - These estimates are similar to VE observed with IIV in children in recent seasons[1-3]
- Differences compared to CDC VE LAIV4 estimate may be due to limited sample, statistical power, and limitations of observational study design
- AstraZeneca/MedImmune will share available 2015-16 VE data with US HCPs to inform discussions of 2016-17 vaccine options with patients
- Research underway to improve LAIV A/H1N1pdm09 strains in future seasons

1. Ohmit et al, CID 2013. 2. McLean et al, JID, 2014. 3. Flannery B. ACIP presentation. December 2014.

Additional Slides

ICICLE 2015-16: No Evidence of Reduced VE with Prior Year Vaccination



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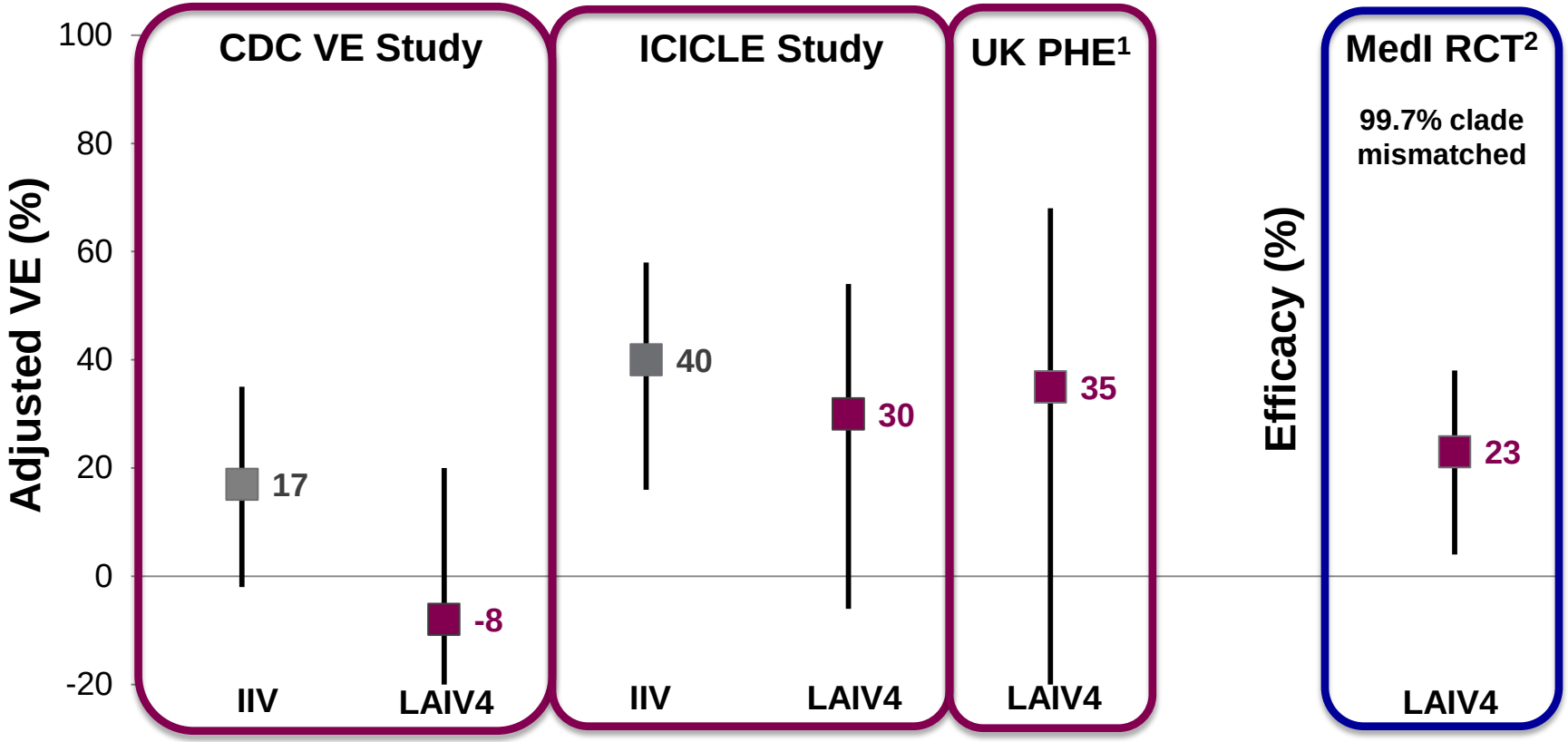
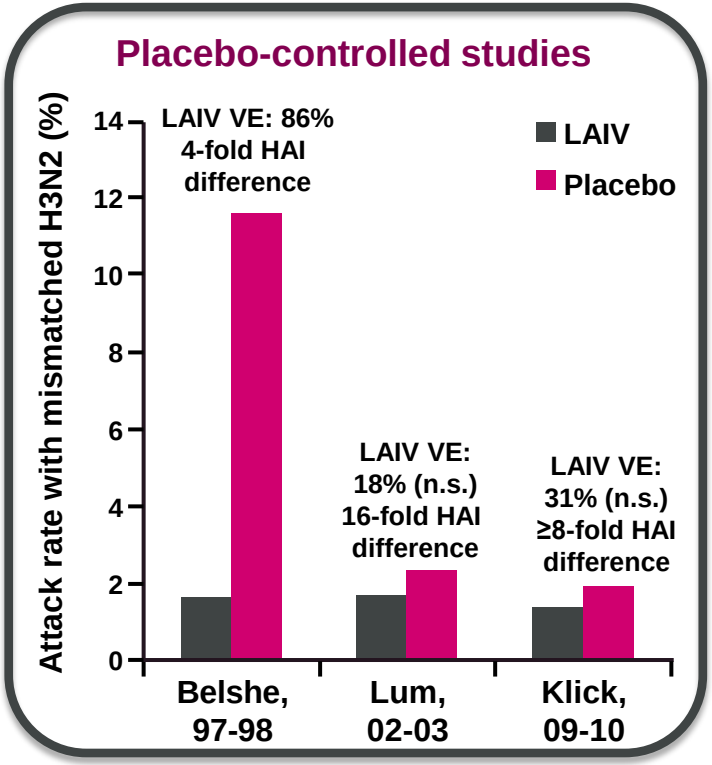
2014-15 A/H3N2 VE of LAIV and IIV in Children

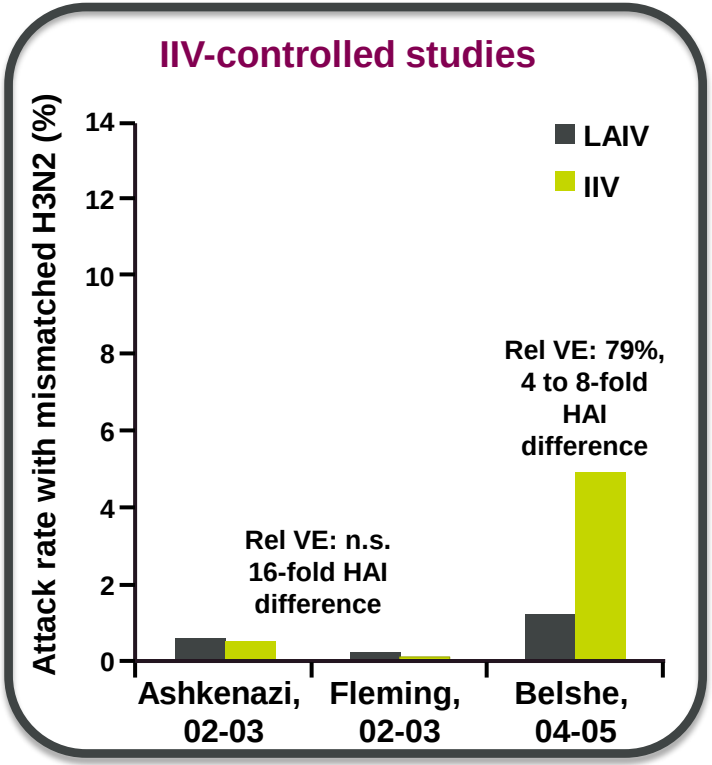


CDC data based on most recent ACIP presentation. ICICLE estimate based on pending publication. 1. Pebody et al, Eurosurveillance, 2015. 2. Randomized, placebo-controlled efficacy study in 1301 children 7-18 years in Japan; 364 of 365 A/H3N2 viruses were mismatched. CI's truncated at -20 to enable graphical display.

LAIV3 Efficacy Against Mismatched A/H3N2 by Antigenic Distance

Mismatched A/H3N2 Attack Rates from 6 Randomized Studies



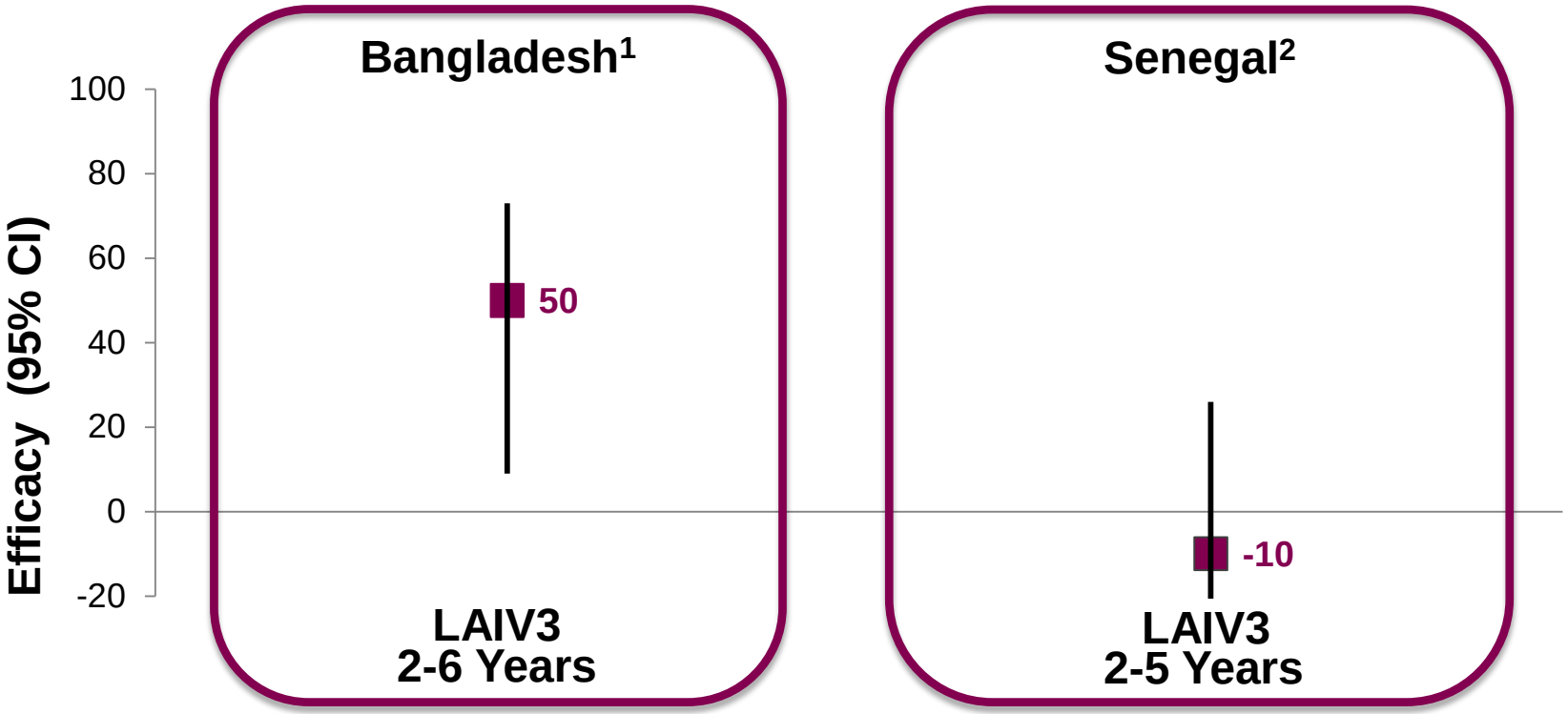


2013-14 Cluster-Randomized Trial of LAIV in Canadian Children

- RELATIVES Study: Cluster-randomized trial of LAIV and IIV in elementary school children in Ontario and their households
- 95% of influenza cases detected were A/H1N1pdm09
- Influenza incidence in children significantly lower with LAIV vs. IIV (0.13 vs 1.24 per 1000 person-days), $p<0.05$

Kwong J, et al. Vaccine 2015.

Two Randomized Trials of A/Leningrad LAIV Against A/H1N1pdm09 in 2013



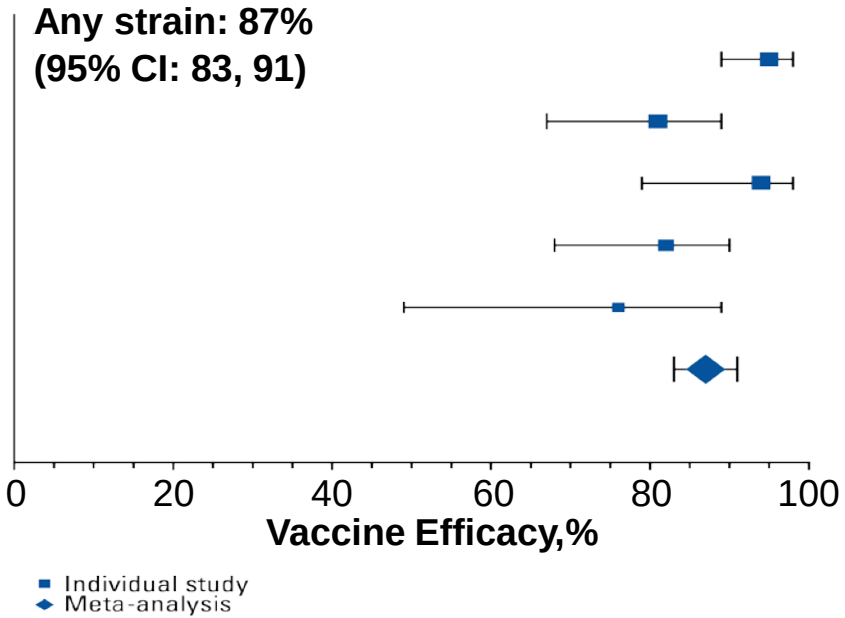
Results of two randomized, placebo-controlled studies conducted in 2013-14 with A/Leningrad LAIV. The Russian A/Leningrad LAIV uses a different master donor virus backbone and is not manufactured by AstraZeneca.

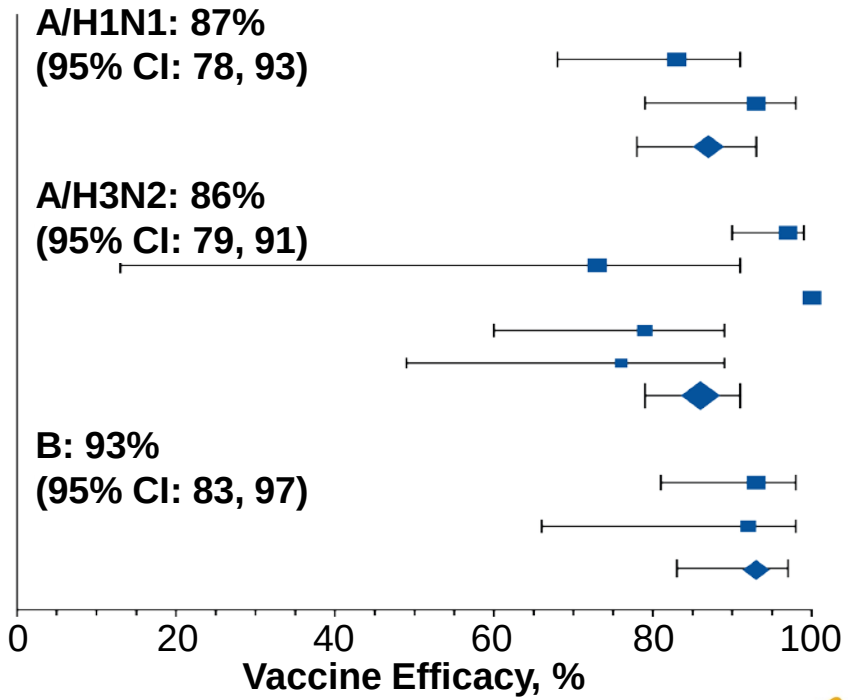
[1] Brooks W, et al. Abstract from XVII International Symposium on Respiratory Viral Infections, March 2015.

[2] Victor J, et al. Abstract from XVII International Symposium on Respiratory Viral Infections, March 2015.

LAIV3 Efficacy in Children in Randomized Trials

5 Randomized Studies in 4,288 Children 2-7 Years, Results for Matched Strains





Ambrose et al., *Vaccine*, 2012.