

# **Update on Effectiveness of Live-Attenuated Versus Inactivated Influenza Vaccines in Children and Adolescents Aged 2–18 Years – US Flu VE Network**

**Brendan Flannery, PhD  
Influenza Division, CDC  
For the US Flu VE Network**

**ACIP, Atlanta, GA  
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# US Flu VE Network contributors

- **University of Michigan and Henry Ford Health System:** Arnold S. Monto, MD, Suzanne E. Ohmit, DrPH, Joshua G. Petrie, MPH, Emileigh Johnson, Rachel T. Cross, MPH, Casey Martens, Marcus Zervos, MD, Lois Lamerato, PhD, Mary Ann Aubuchon, William Fredrick;
- **University of Pittsburgh Schools of the Health Sciences and UPMC:** Richard K. Zimmerman, MD, Mary Patricia Nowalk, PhD, Jonathan M. Raviotta, MPH, Heather Eng, Stephen R. Wisniewski, PhD, Charles R. Rinaldo, Jr, MD, Arlene Bullotta, Joe Suyama, MD, Evelyn Reis, MD, Donald B. Middleton, MD, Rhett H. Lieberman, MD, Michael Susick, MPH, Krissy K. Moehling, MPH, Mallory Schaffer, BS;
- **Baylor Scott and White Health, Texas A&M University Health Science Center College of Medicine:** Manjusha Gaglani, MBBS, Lydia Clipper, RN, Anne Robertson, AA, Kempapura Murthy, MPH, Monica Weir, Hope Gonzales, Martha Zayed, Teresa Ponder, Virginia Gandy, RN, Patricia Sleeth, RN, Sophia V James, MS, , Michael Reis, MD, Cathleen Rivera, MD, David Morgan, MD, and Baylor College of Medicine : Pedro Piedra, MD, Vasanthi Avadhanula, PhD;
- **Group Health Research Institute :** Michael L. Jackson, PhD, Lisa A. Jackson, MD, C. Hallie Phillips, MEd, Joyce Benoit, RN, Lawrence T. Madziwa, MS, Matt B. Nguyen, MPH, Julia P. Anderson, MA;
- **Marshfield Clinic Research Foundation:** Edward A. Belongia, MD, Huong Q. McLean, PhD, Deanna Cole, Donna David, Sarah Kopitzke, MS, Tamara A. Kronenwetter Koepel, Jennifer K. Meece, PhD, Carla Rottscheit, Sandra K. Strey, Maria E. Sundaram, MSPH, Jennifer King, MPH, Laurel A. Verhagen;
- **Influenza Division, CDC:** Alicia Fry, MD, Swathi N. Thaker, PhD, Jessie Clippard, MPH, Sarah Spencer, PhD, Ivo Foppa, PhD, Jill Ferdinands, PhD, LaShondra Berman, MS, Angie Foust, MS, Wendy Sessions, MPH, Erin Burns, MA, Joseph Bresee, MD, Dan Jernigan, MD, Nancy Cox, PhD.

# US Flu VE Network: 5 Sites and Principal Investigators

Group Health  
Cooperative  
**Lisa Jackson**  
**Mike Jackson**

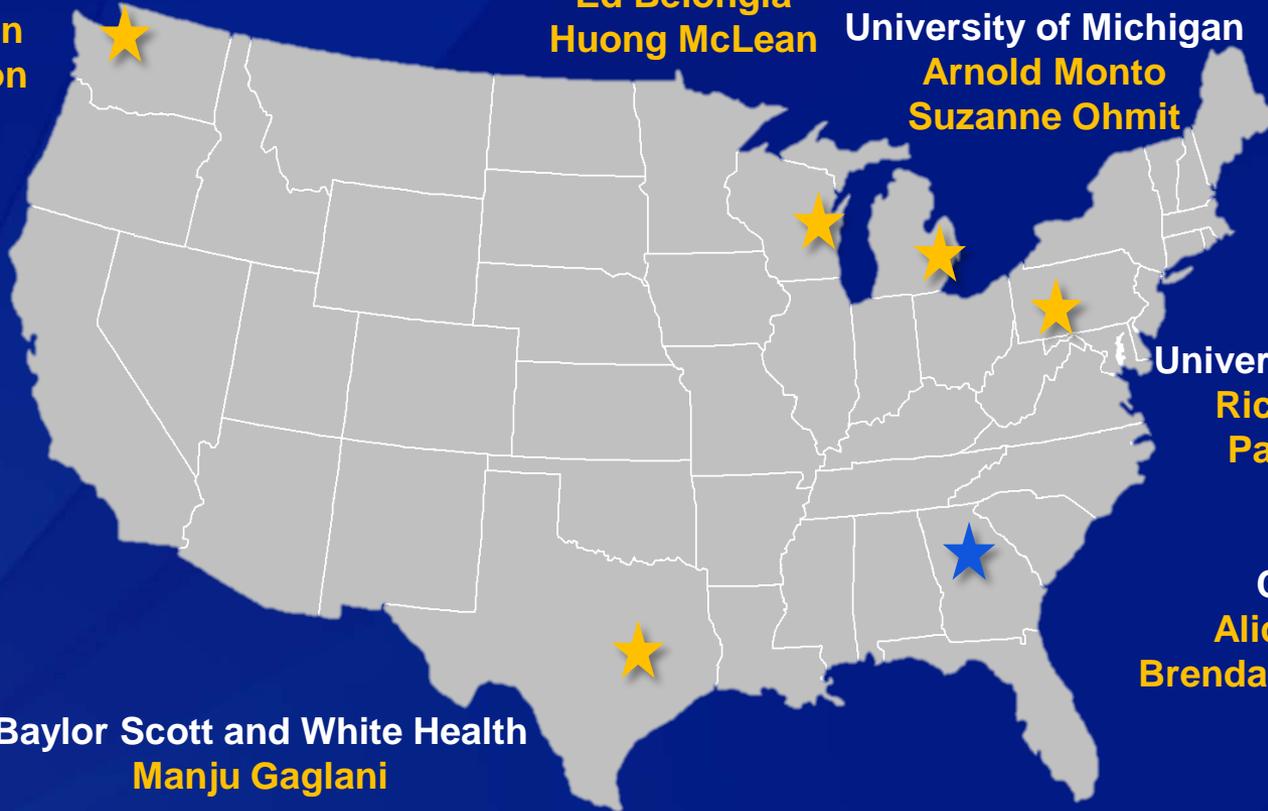
Marshfield Clinic Research  
Foundation  
**Ed Belongia**  
**Huong McLean**

University of Michigan  
**Arnold Monto**  
**Suzanne Ohmit**

University of Pittsburgh  
**Rick Zimmerman**  
**Patricia Nowalk**

CDC  
**Alicia Fry**  
**Brendan Flannery**

Baylor Scott and White Health  
**Manju Gaglani**



## Objectives

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- ❑ **Compare LAIV and IIV vaccine effectiveness (VE) among children and adolescents during 3 influenza seasons: 2011-12, 2012-13, and 2013-14**
- ❑ **Summarize other data from observational studies evaluating LAIV and IIV among children in 2013-14**

# Methods: US Flu VE Network

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**Enrollees:** Outpatients aged  $\geq 6$  months with acute respiratory illness with cough  $\leq 7$  days duration

**Methods:** Prospective case-control study (test-negative design)

- ❑ All enrolled outpatients tested for influenza by RT-PCR
  - Cases: Outpatients with confirmed influenza
  - Controls: Outpatients without influenza (PCR-negative)
- ❑ Vaccination status: confirmed by medical record or registry
  - Includes only fully vaccinated per ACIP recommendations  $\geq 14$  days before illness onset
- ❑ **Analysis:**  $VE = (1 - \text{adjusted OR}) \times 100\%$ 
  - Adjusted for: age, sex, site, days from illness onset to enrollment, high-risk health status, calendar time (2- week intervals), race/ethnicity and parental-rated general health

# Analysis Methods

## □ Inclusion Criteria

- 2–18 years of age
- Received only one type of vaccine within season (LAIV or IIV)

## □ VE of LAIV: LAIV vs no vaccine

- Excludes subjects 2–18 y who received IIV for that season

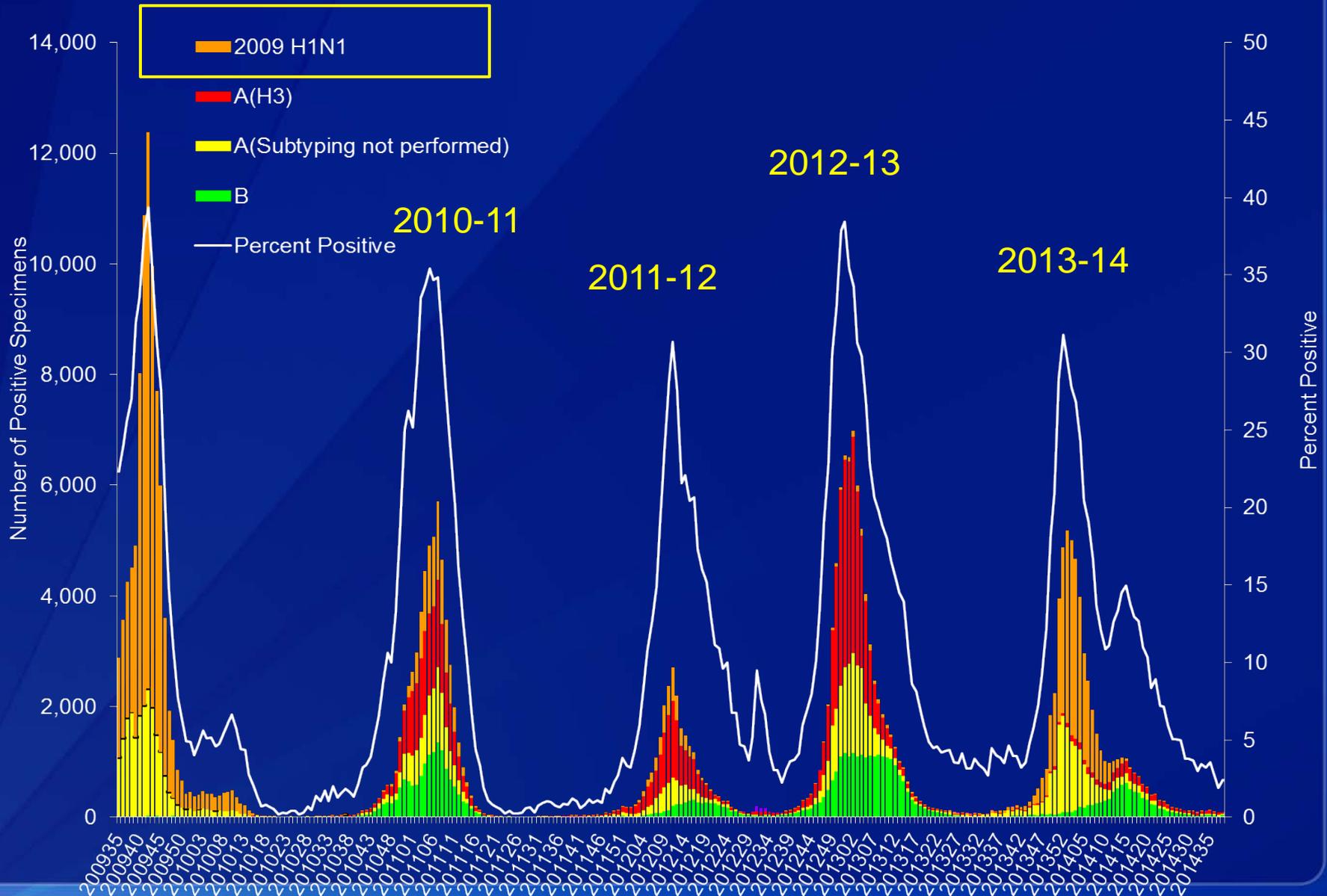
## □ VE of IIV: IIV vs no vaccine

- Excludes subjects 2–18 y who received LAIV for that season

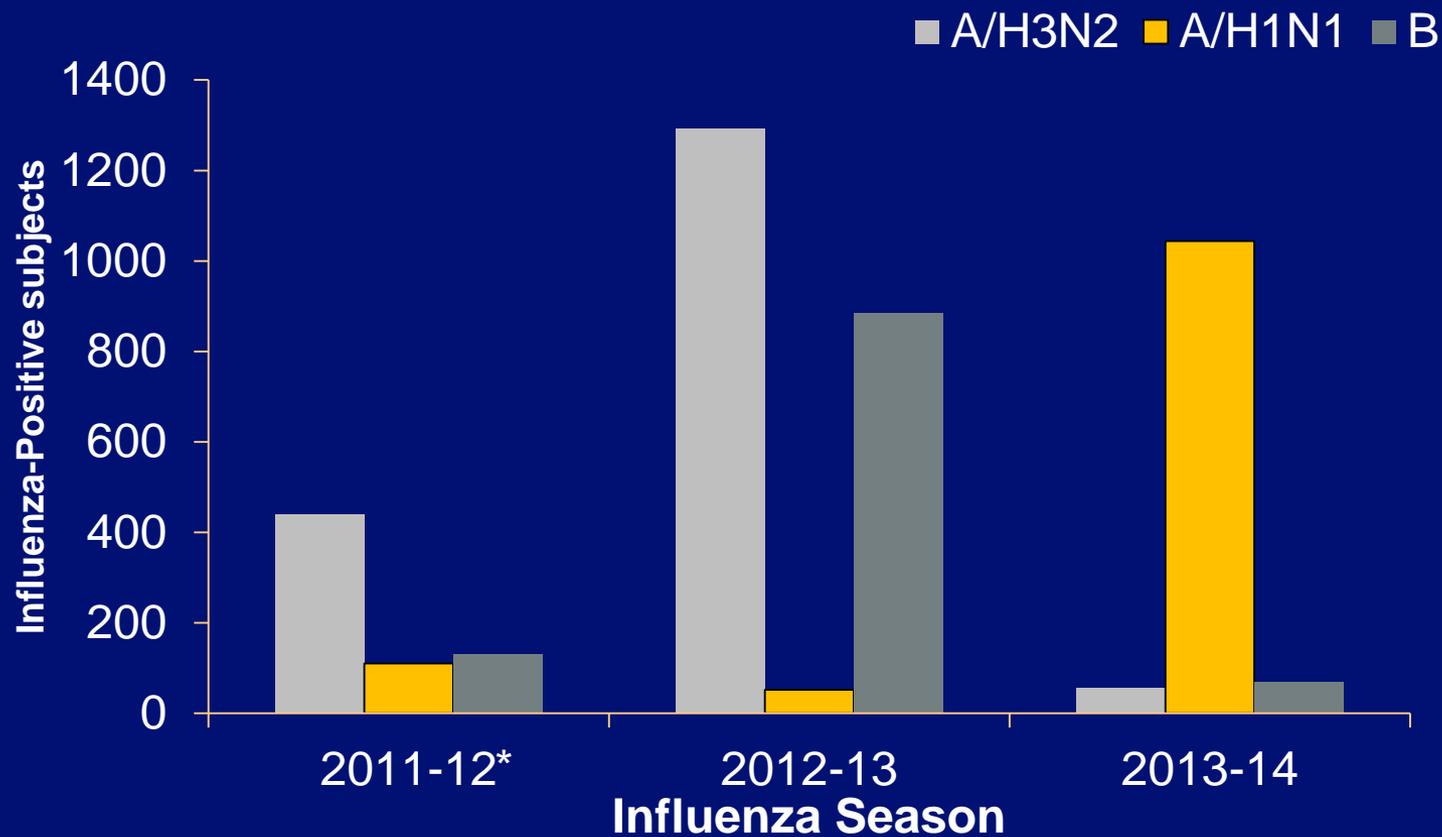
## □ Relative effectiveness of LAIV to IIV: LAIV vs IIV

- Excludes unvaccinated subjects 2–18 y for that season

# U.S. WHO/NREVSS Collaborating Laboratories, National Summary, 2009-14



# Distribution of influenza virus type/subtypes among influenza-positive cases in US Flu VE Network, past 3 influenza seasons

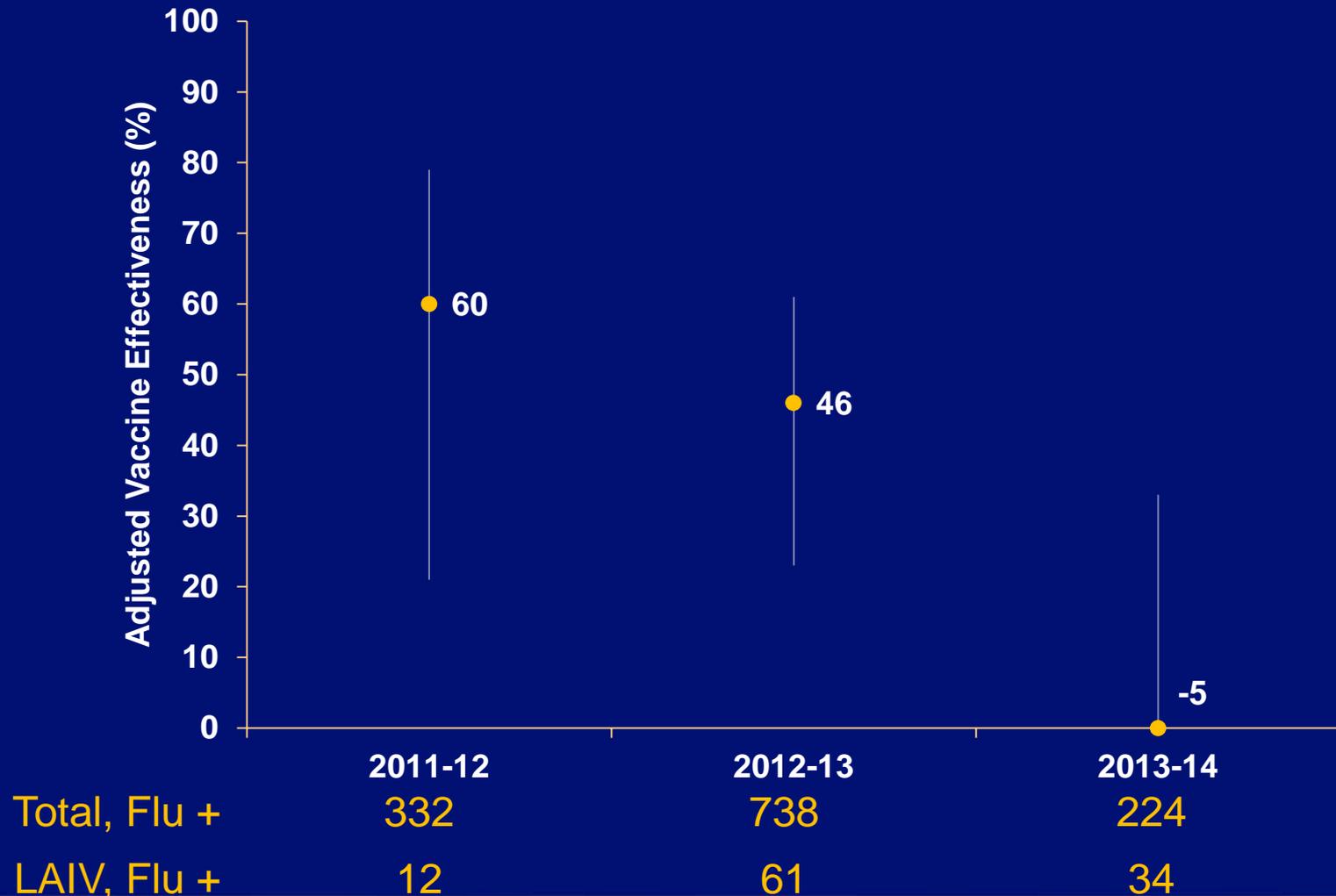


\*Ohmit et al. CID 2013

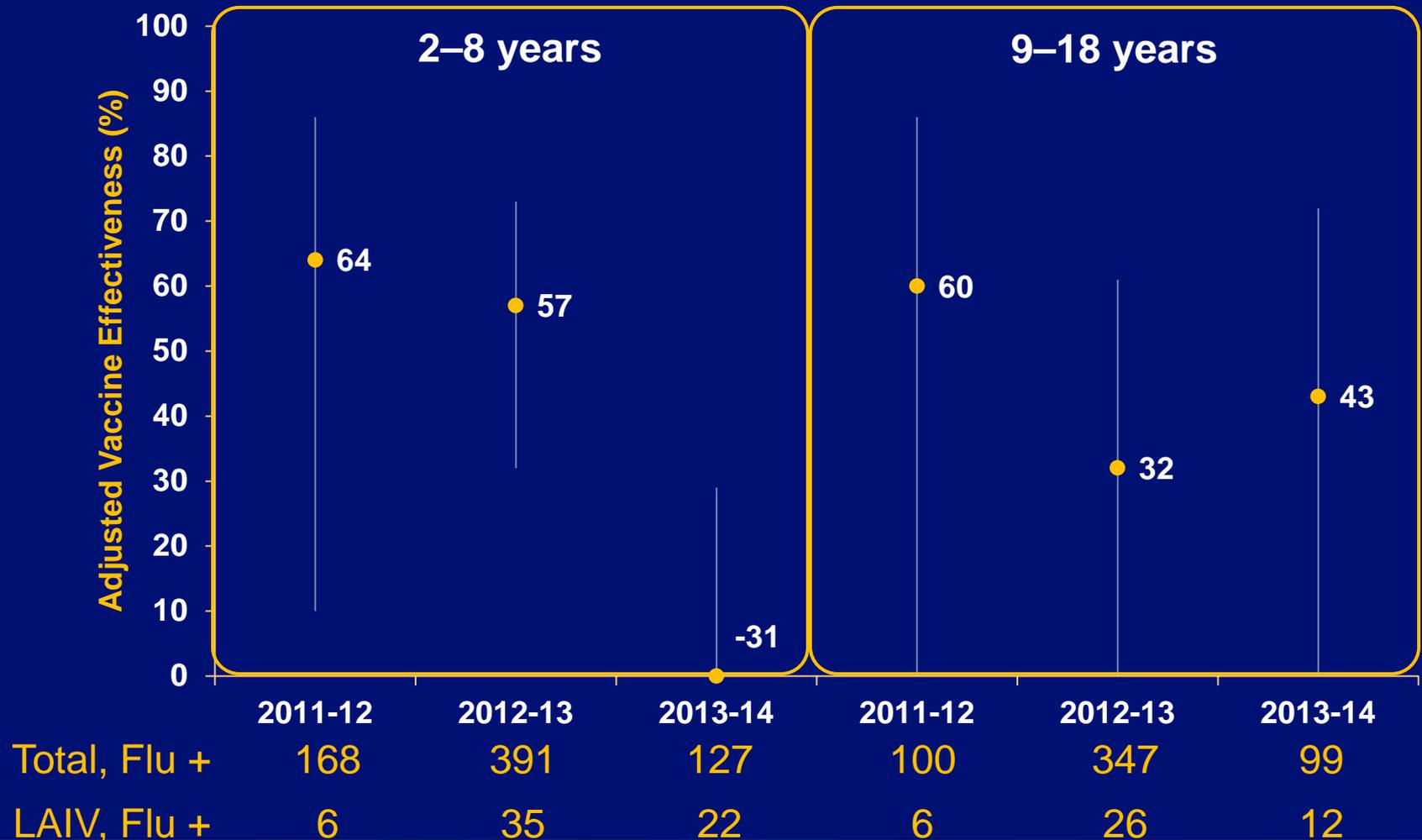
**Vaccine effectiveness (VE)**

**Live-attenuated influenza vaccine (LAIV)**

# LAIV effectiveness against medically-attended influenza among 2–18 yr olds, US Flu VE Network



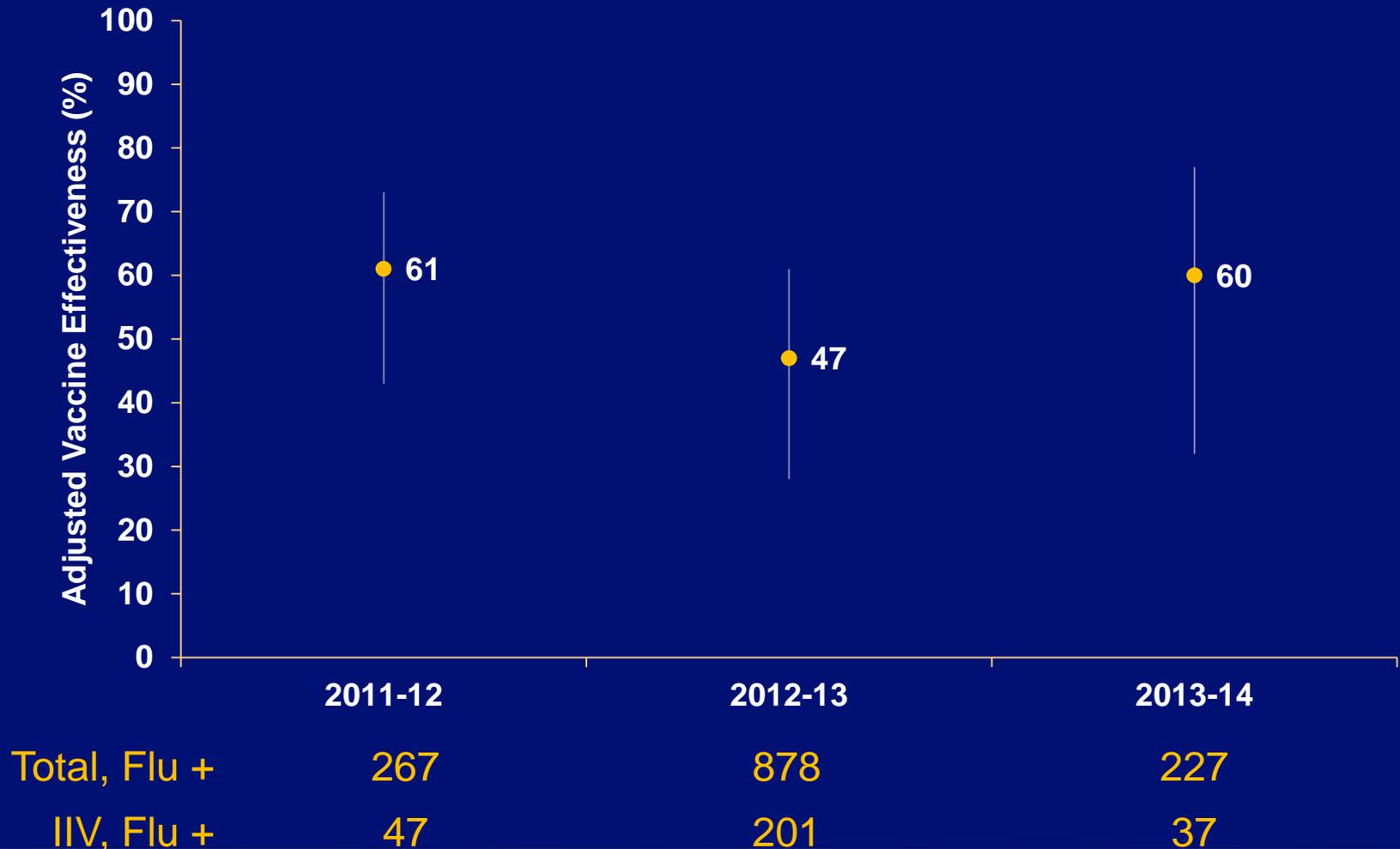
# LAIV effectiveness against medically-attended influenza, by season and age category



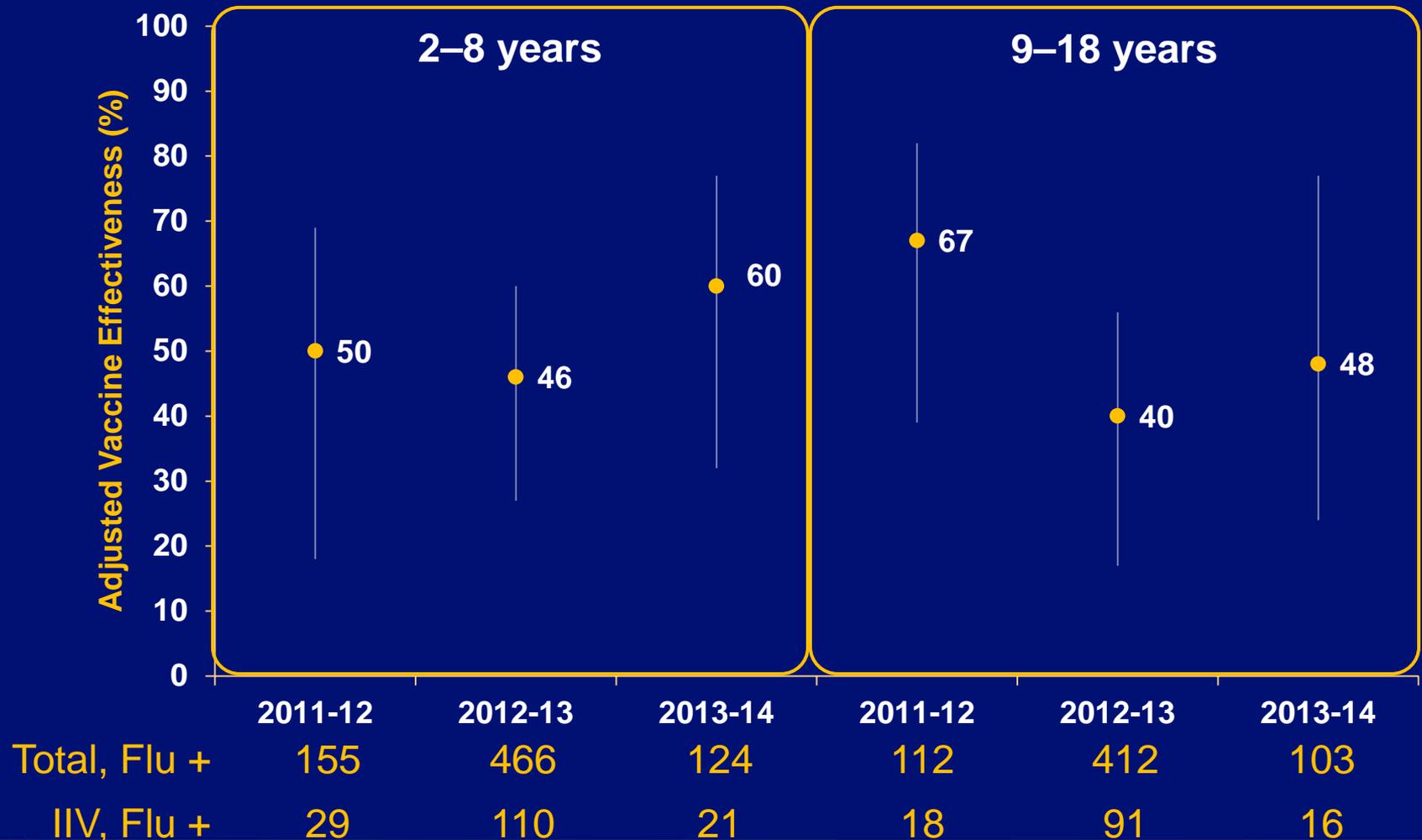
**Vaccine effectiveness (VE)**

**Inactivated influenza vaccines (IIV)**

# IIV effectiveness against medically-attended influenza among 2–18 yr olds, US Flu VE Network

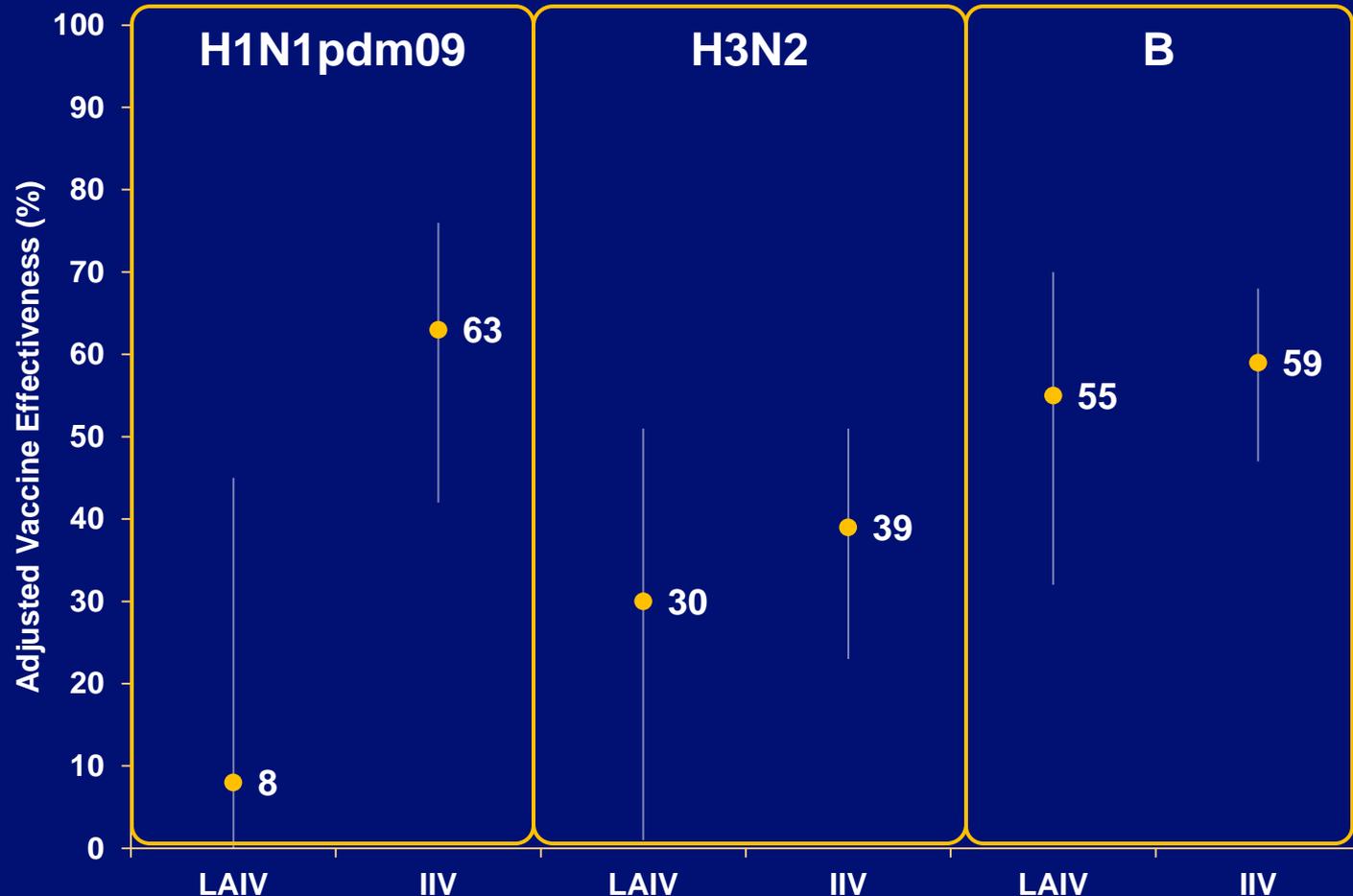


# IIV effectiveness against medically-attended influenza, by season and age category



# **LAIV and IIV vaccine effectiveness by influenza type/subtype**

# LAIV and IIV vaccine effectiveness among 2-18 yrs over 3 seasons, by influenza type/subtype



Total, Flu +

LAIV  
184

IIV  
188

LAIV  
493

IIV  
596

LAIV  
472

IIV  
544

Vaccinated, Flu +

24

28

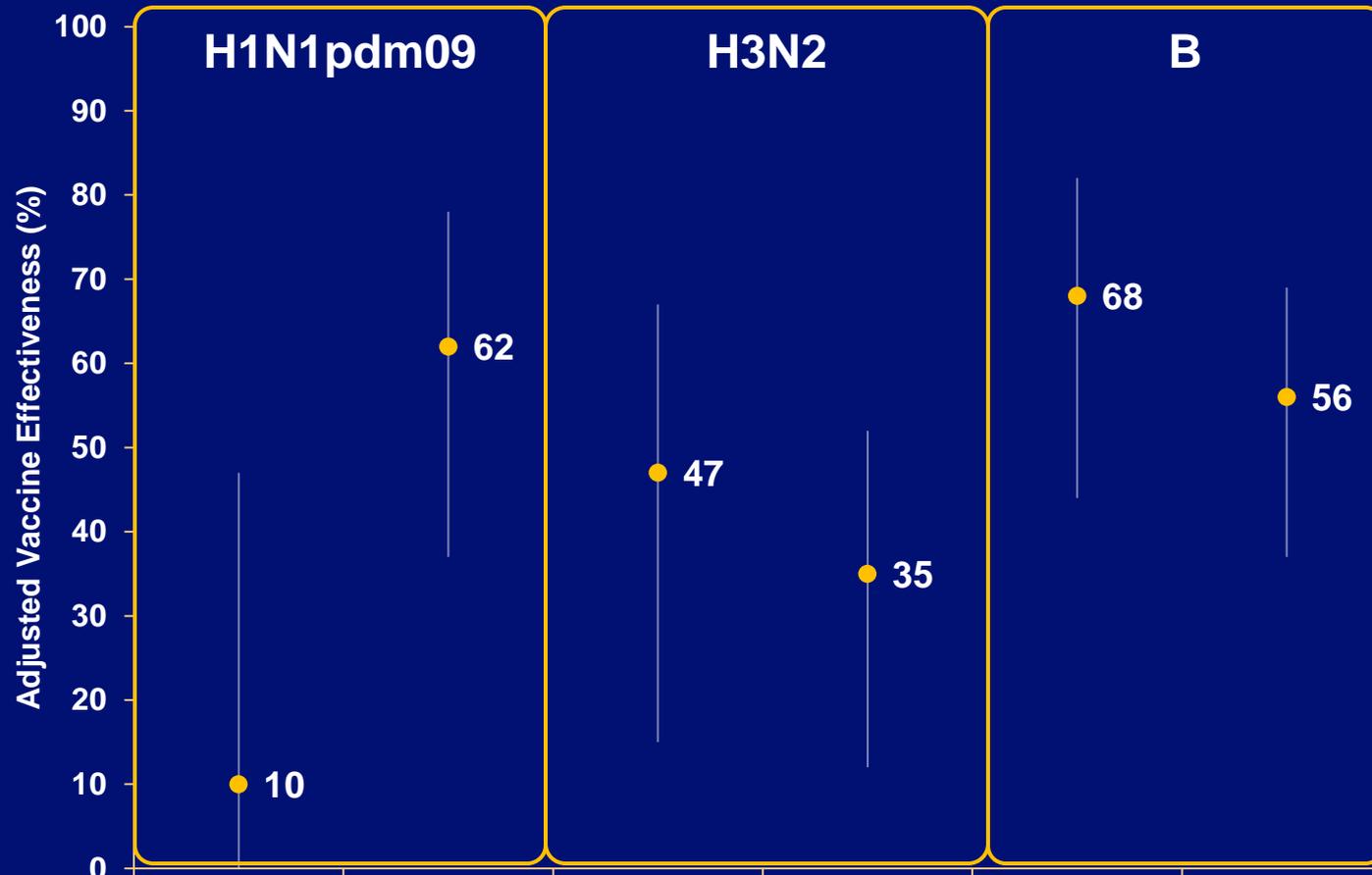
48

151

33

105

# LAIV and IIV vaccine effectiveness among 2-8 yrs over 3 seasons, by influenza type/subtype

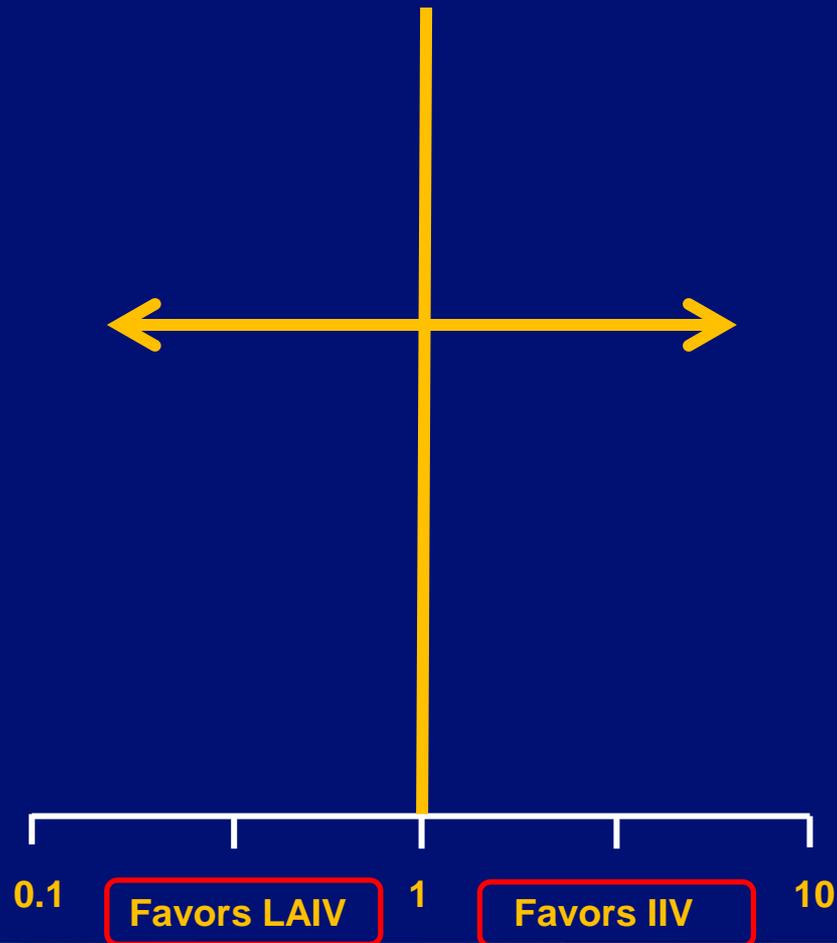


	LAIV	IIV	LAIV	IIV	LAIV	IIV
Total, Flu +	111	112	265	321	249	290
Vaccinated, Flu +	17	18	27	83	17	58

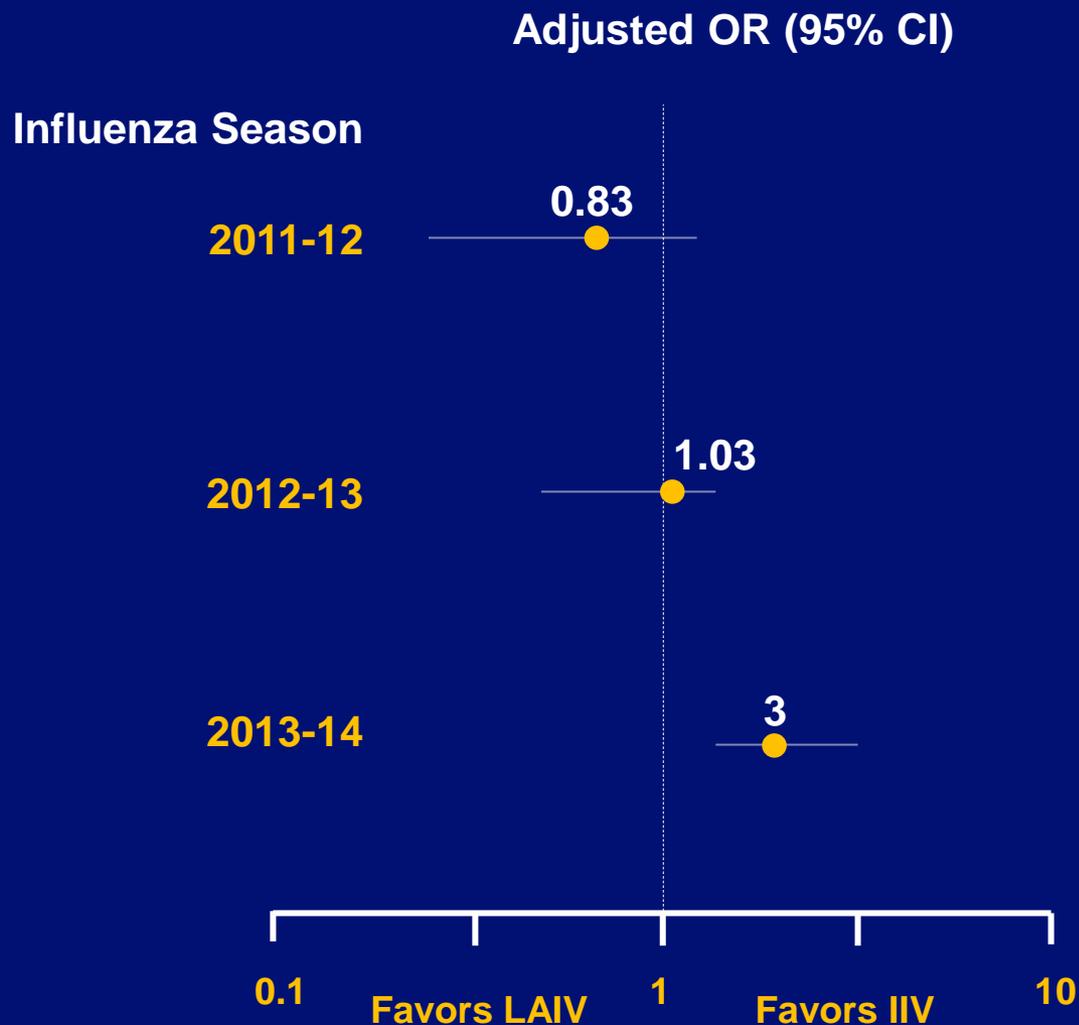
# **Relative effectiveness of LAIV to IIV**

# Relative effectiveness of LAIV to IIV against medically-attended influenza

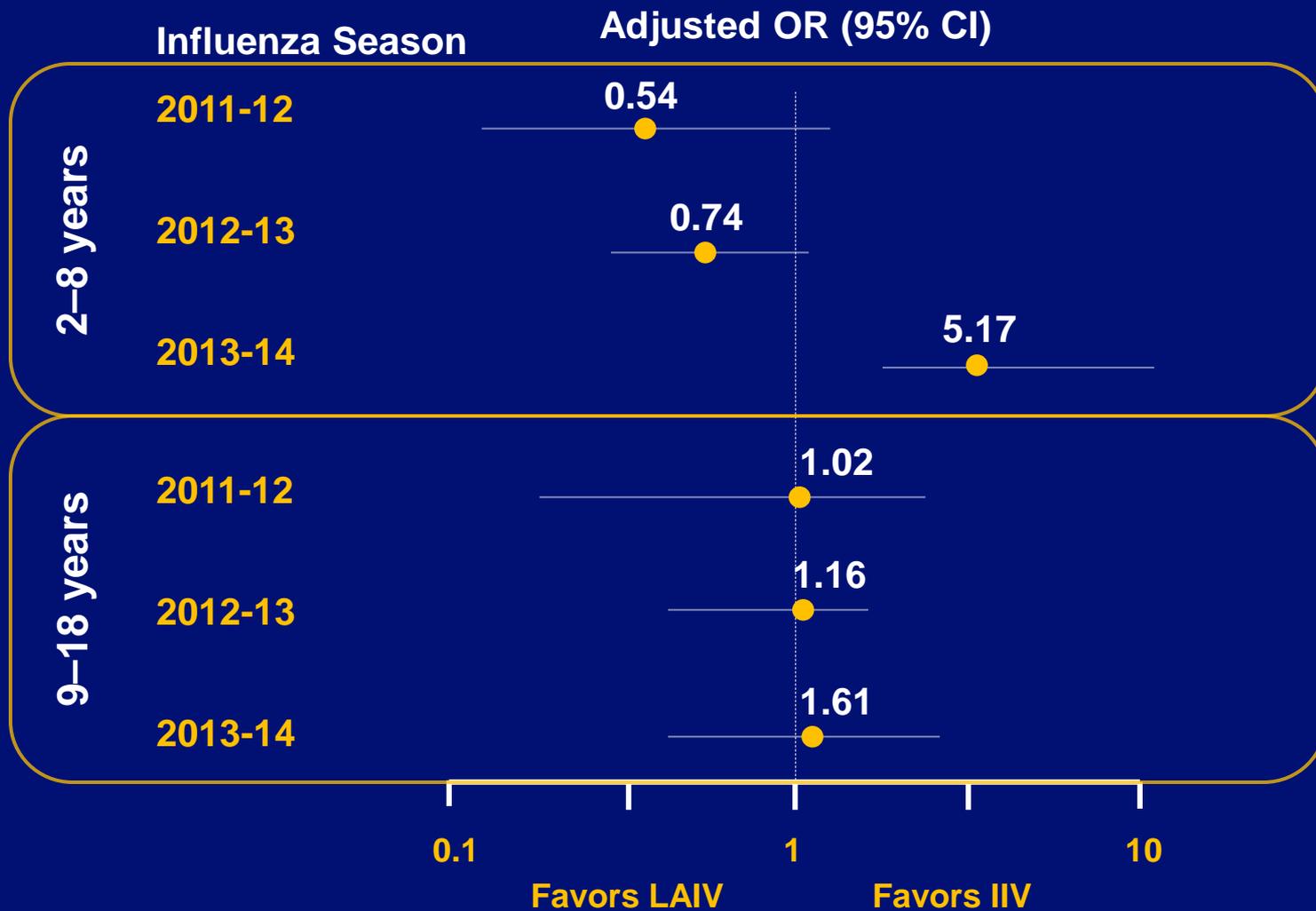
Adjusted OR (95% CI)



# Relative effectiveness of LAIV to IIV, aged 2-18 yrs over past 3 influenza seasons, US Flu VE Network



# Relative effectiveness of LAIV to IIV during past 3 influenza seasons, by age group



# Limitations

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- ❑ **Single season vs. H1N1 vaccine virus?**
  - Limited circulation of H1N1pdm09 in US Flu VE Network from 2010-2013
- ❑ **Ability to measure VE among children by vaccine type (LAIV vs IIV) depends on vaccine uptake and requires large sample size**
  - Limited ability to control for potential confounding variables

## Summary: US Flu VE Network

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- ❑ During 2011-12 and 2012-13, relative effectiveness favored LAIV versus IIV in young children but was not significant
- ❑ During 2013-14, relative effectiveness favored IIV versus LAIV in young children
- ❑ H1N1pdm09 was predominant virus for the first time during 2013-14
  - Subtype analysis is consistent with low VE for LAIV against H1N1pdm09
  - Cannot rule out specific issue related to 2013-14, e.g. study enrollees or design, unmeasured confounding, or vaccine issue

**Review of additional data from 2013-14  
season on LAIV and IV effectiveness in  
children and adolescents**



## LAIV Effectiveness Study

### Preliminary Results from 2013-2014

October 20, 2014

Chris Ambrose, M.D.

Vice President, US Medical Affairs

# Summary of MedImmune Study Findings

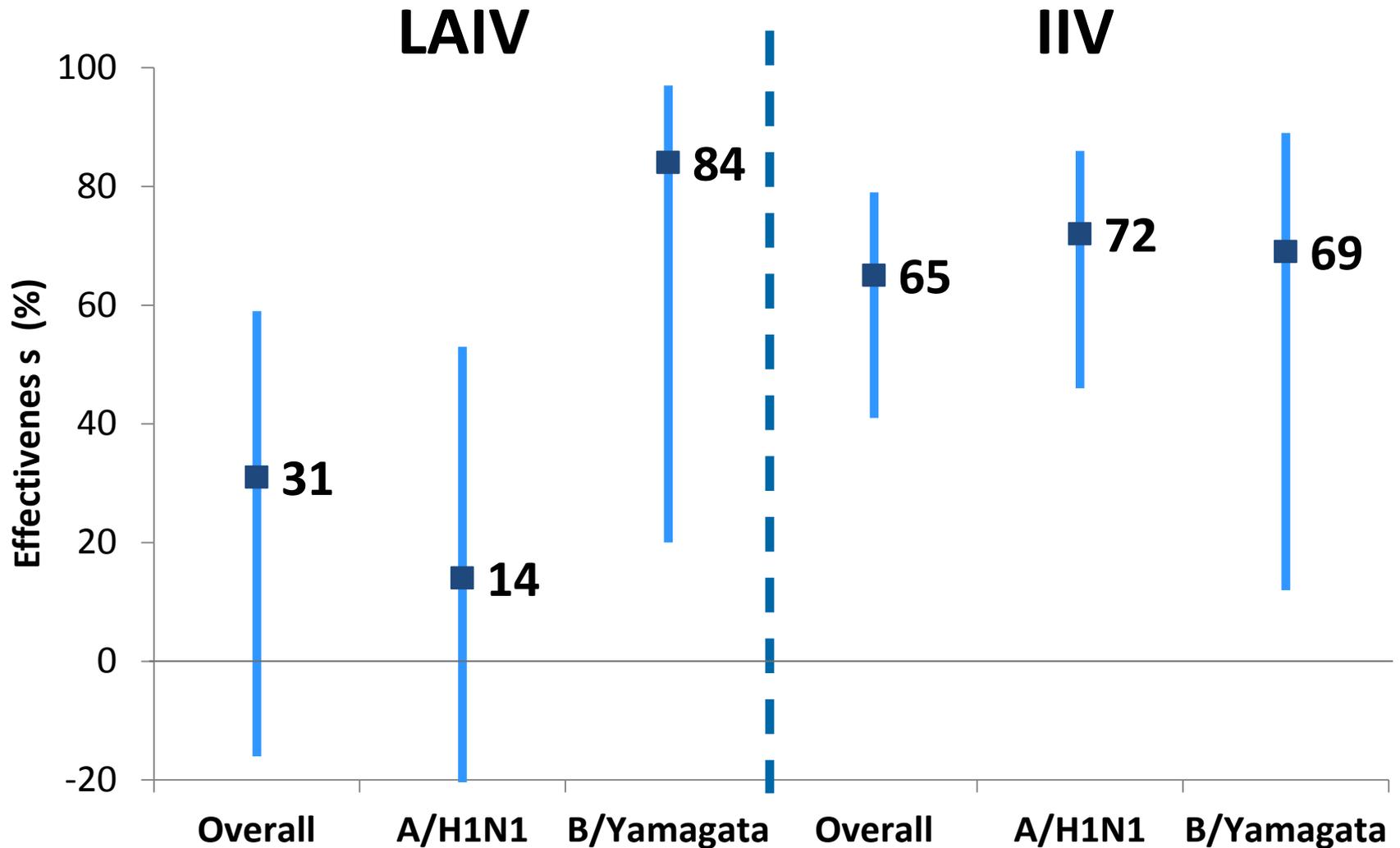
- ◆ MedImmune study results are similar to CDC results
  - High LAIV effectiveness for influenza B
  - No significant effectiveness for A/H1N1 overall
- ◆ Significant differences in effectiveness observed by vaccine lot shipping time
- ◆ No clear explanation at present; comprehensive investigations into potential explanations are ongoing
- ◆ Differences by lot might be explained by H1N1 strain potency loss
  - A/California LAIV more susceptible to thermal degradation due to unique HA stalk sequence<sup>1</sup>
  - Sequence not present in seasonal influenza LAIV strains

1. Cotter et al, PLoS Pathogens, 2014

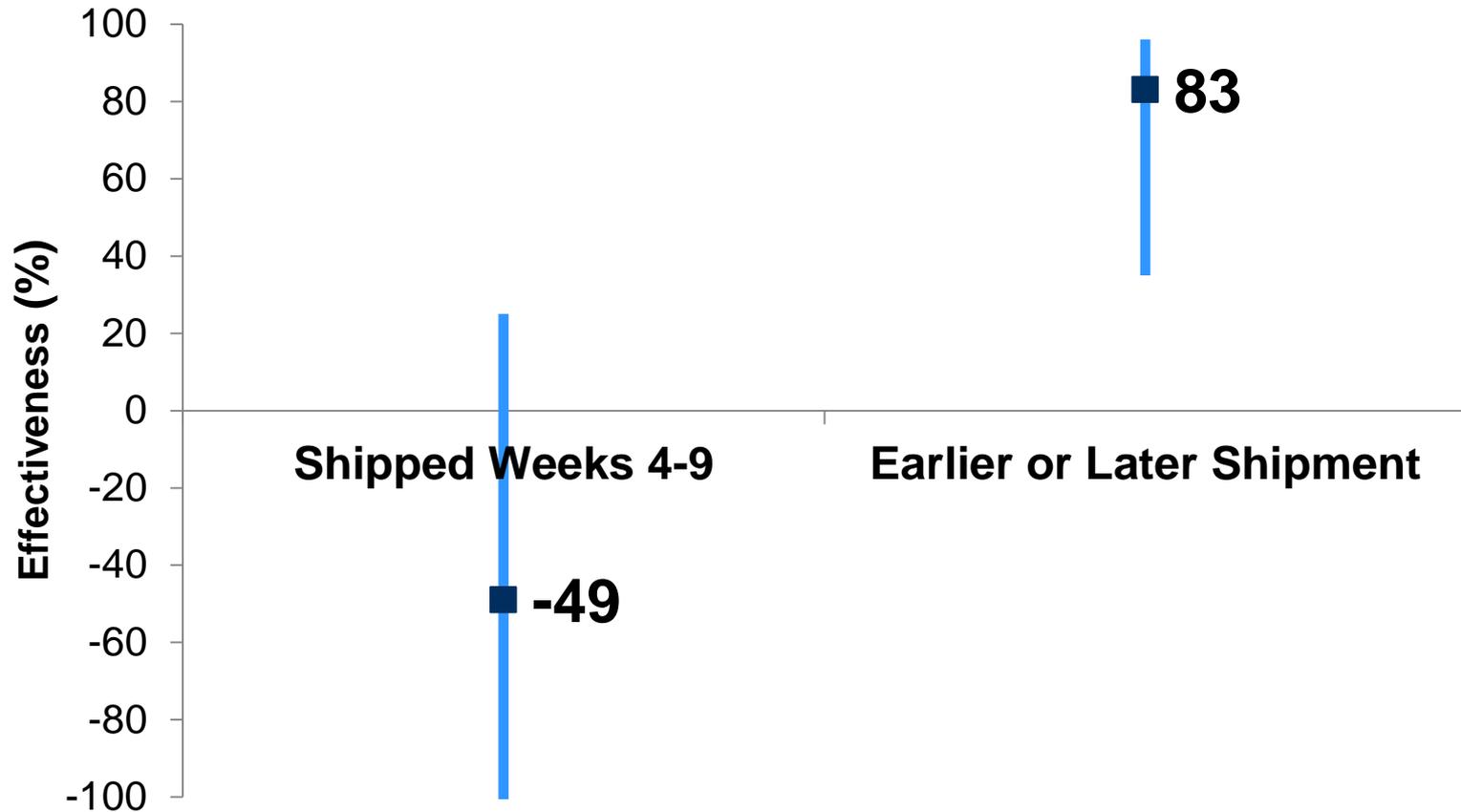
# MedImmune Study of LAIV effectiveness

- ◆ Community-dwelling children 2-17 years of age
  - Vanderbilt/Tennessee (Marie Griffin)
  - Wake Forest/North Carolina (Katherine Poehling)
  - Scott and White/Texas (Manjusha Gaglani)
  - Marshfield Clinic/Wisconsin (Edward Belongia)
- ◆ Similar study design to CDC study
- ◆ Enrolled 1082 children; 1033 available for analysis

# MedImmune Study: Adjusted Estimates of Absolute Effectiveness



# MedImmune Study: Adjusted LAIV H1N1 Effectiveness by Shipment Group



➤ Not explained by any other study covariates



# Influenza Vaccine Effectiveness: Air Force Children, 2013- 2014 Influenza Season

Angelia Cost, PhD, ScM  
Senior Managing Epidemiologist  
Epidemiology & Analysis  
Armed Forces Health Surveillance  
Center  
[Angelia.a.cost.ctr@mail.mil](mailto:Angelia.a.cost.ctr@mail.mil)

# Methods



- Time Period:
  - Vaccinations: 01AUG2013 - 31MAY2014
  - Outcomes: 01SEP2013 - 31MAY2014
- Population: Air Force dependents 2-17 years of age
  - Only service with database of dependent immunizations
- Case / Test-negative control design
  - Lab-confirmed influenza cases (PCR, culture, or rapid)
  - Test negative controls (PCR or culture only; rapid negative test excluded)
- Considered vaccinated if vaccine received at least 14 days prior to lab test



# Summary of Findings

- Moderate VE found for any vaccine type and IIV for all age groups (not statistically significant among 9-17 year olds)
- Low to negative, non-statistically significant VE for LAIV among all age groups
- Low LAIV VE may be related to predominance of A/H1 circulation this season
  - Subtype analysis overall and among 2-8 year olds revealed LAIV VE point estimates moderate for A/H3, but not for A/H1 (none were statistically significant)



## Summary of observational data

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- ❑ **3 US studies during 2013-14 season using test-negative design reported low VE for LAIV4**
  - All 3 reported higher and significant VE for IIV among children/adolescents
- ❑ **All 3 studies reported low VE (nonsignificant) for LAIV4 against H1N1pdm09 in 2013-14**
- ❑ **MedImmune post-licensure study reported significant VE for LAIV4 (similar to IIV) against influenza B-Yamagata, but not H1N1pdm09**

# Thank you.

**For more information please contact Centers for Disease Control and Prevention**

1600 Clifton Road NE, Atlanta, GA 30333

Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348

Visit: [www.cdc.gov](http://www.cdc.gov) | Contact CDC at: 1-800-CDC-INFO or [www.cdc.gov/info](http://www.cdc.gov/info)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

National Center for Immunization & Respiratory Diseases  
Influenza Division



## **GRADE of LAIV and IIV for Healthy Children Aged 2 through 8 years**

- ❑ **Several studies suggested potential advantages of LAIV over IIV for children, including better vaccine efficacy and heterotypic protection.**
- ❑ **Several countries (Canada, the United Kingdom, Israel, Germany) and two U.S. states (Washington, Oregon) previously expressed some degree of LAIV preference for young children.**
- ❑ **In June 2014, ACIP recommended that LAIV should be used when available for healthy children aged 2 through 8 years, following GRADE assessment of data from 2 comparative RCTs.**

# 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	0.46 [0.39 – 0.54]	43 fewer per 1000 [37 – 49 fewer]	⊕⊕⊕⊕ High



- **Influenza cases included all influenza types/subtypes**
  - All A(H1N1), A(H3N2), and B
  - Without regard to antigenic similarity to viruses in vaccine

# Type/Subtype- and Match-specific Relative VE (1)

## Belshe, 2007 (2004-05 season)

- ❑ Randomized, placebo-blinded comparative trial of LAIV and IIV
  
- ❑ All H1N1 antigenically matched vaccine (A/New Caledonia/20/1999)
  - Relative VE (LAIV vs. IIV): 89.2 (95%CI, 67.7—97.4)
  
- ❑ All H3N2 were antigenically mismatched (drifted)
  - Relative VE (LAIV vs. IIV): 79.2 (95%CI, 70.6—85.7)
  
- ❑ B viruses from both lineages (some matched vaccine, some not)
  - Relative VE (LAIV vs IIV, matched): 27.3 (95%CI, -4.8—49.9)
  - Relative VE (LAIV vs. IIV, mismatched): 6.3 (95%CI, -31.6—33.3)

## Type/Subtype- and Match-specific Relative VE (2)

### Ashkenazi, 2006 (2002-03 season)

- ❑ Randomized, open-label comparative trial of LAIV and IIV
- ❑ Cases included
  - A(H1N1), A(H3N2) and B viruses regarded as antigenically similar to vaccine, and
  - Some H3N2 regarded as antigenically distinct from vaccine.
- ❑ Vaccine A(H1N1) was A/New Caledonia/20/1999
- ❑ Results specific to mismatched strains not reported
- ❑ Type/subtype-specific, without regard to match, relative (LAIV vs. IIV) VE
  - A(H1N1):           100       (95%CI, 56.0—100)
  - A(H3N2):           -47.9     (95%CI, -236.5—32.6)
  - B:                    68.9     (95%CI, 39.2—85.2)

# Summary--VE of LAIV Against A(H1N1)pdm09

- ❑ **Comparative studies of LAIV and IIV were conducted prior to 2009 pandemic**
  - No H1N1pdm09-specific efficacy data available from RCTs
  - Relatively little effectiveness data for monovalent LAIV
  
- ❑ **2013-14 was first H1N1-predominant influenza season since 2009 pandemic**
  - First clear indication of suboptimal effectiveness of LAIV for H1N1pdm09
  
- ❑ **Explanation for 2013-14 findings unknown**
  - Differences by lot shipping time in MedImmune data under investigation
    - But, good VE for LAIV against Influenza B; similar findings in three different datasets
  - Current data are from observational studies; potential confounding
    - However, similar observations in three different datasets

## Summary--VE of LAIV Against A(H1N1)pdm09

- ❑ LAIV H1N1pdm09 may be less stable than seasonal H1N1 LAIV viruses (Cotter et al, 2014 )
  - Sequence in HA stalk confers higher susceptibility to thermal degradation
  - Potentially could affect stability and/or replicative fitness of the vaccine virus
    - Biologically plausible
    - Could be consistent with previous VE observed with seasonal H1N1 and 2013-14 observations of good effectiveness of LAIV against influenza B
  
- ❑ Looking forward
  - 2014-15 vaccine has already been produced—no changes anticipated this season
  - US Flu VE Network receiving resources to increase enrollment of children
  - Work Group will discuss additional data from these and other sources as it becomes available