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# Update on Live Attenuated Influenza Vaccine (LAIV)

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ACIP Meeting

February 25, 2015

# Overall Summary

- Moderate/high effectiveness in children observed in 2010-11, 2011-12, 2012-13, 2013-14 for A/H3N2 and B strains and for all matched strains in prior studies
- Low effectiveness observed for A/California H1N1pdm09 strain in US in 2010-2011 (trivalent formulation) and 2013-2014 (quadrivalent formulation)
  - Issue is specific for A/California H1N1pdm09 LAIV
  - Issue may be US-specific as LAIV appeared effective in Canada in 2013-14
- Low effectiveness of A/California LAIV not explained by
  - Manufacturing, poor stability under recommended storage (36-46°F), antigenic mismatch, prior vaccination, pre-existing immunity, or vaccine strain interference
- A/California H1N1pdm09 strain has unique HA stalk sequence not seen in any previous LAIV strain that makes HA less stable
  - Reduces viral fitness and makes strain more vulnerable to heat degradation
- Vaccine shipping when outdoor temperatures are >80°F correlates with reduced effectiveness for A/California LAIV but not other LAIV strains
- Will replace A/California LAIV with an antigenically matched strain with a more stable HA protein and add HA stability criterion to future strain selection processes

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# 1 LAIV Effectiveness Data

LAIV is indicated for active immunization of persons 2-49 years of age for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. It is for intranasal administration only. LAIV is contraindicated in persons who have had a severe allergic reaction to any vaccine component, including egg protein, or after a previous dose of any influenza vaccine, and in children and adolescents receiving concomitant aspirin or aspirin-containing therapy.

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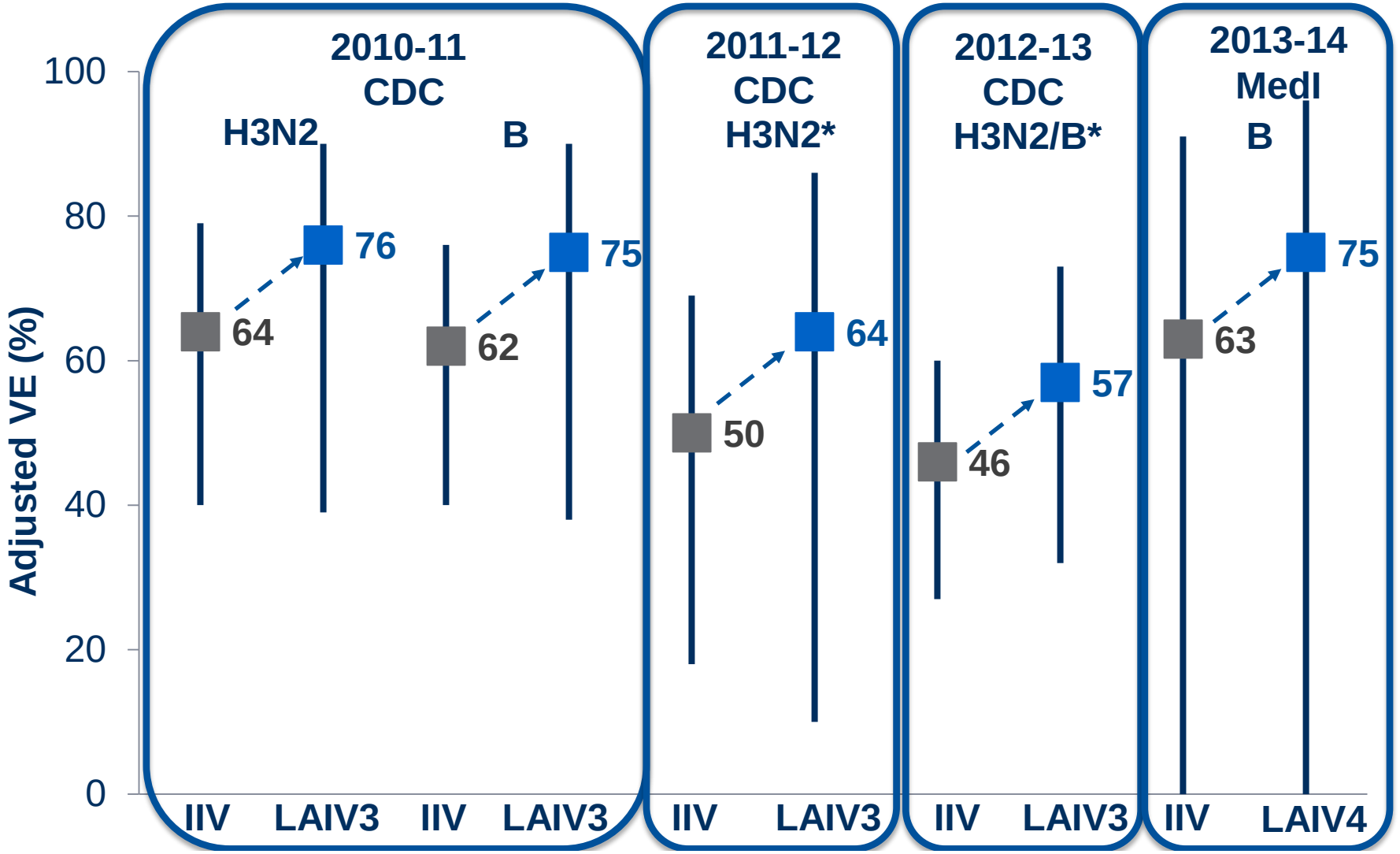
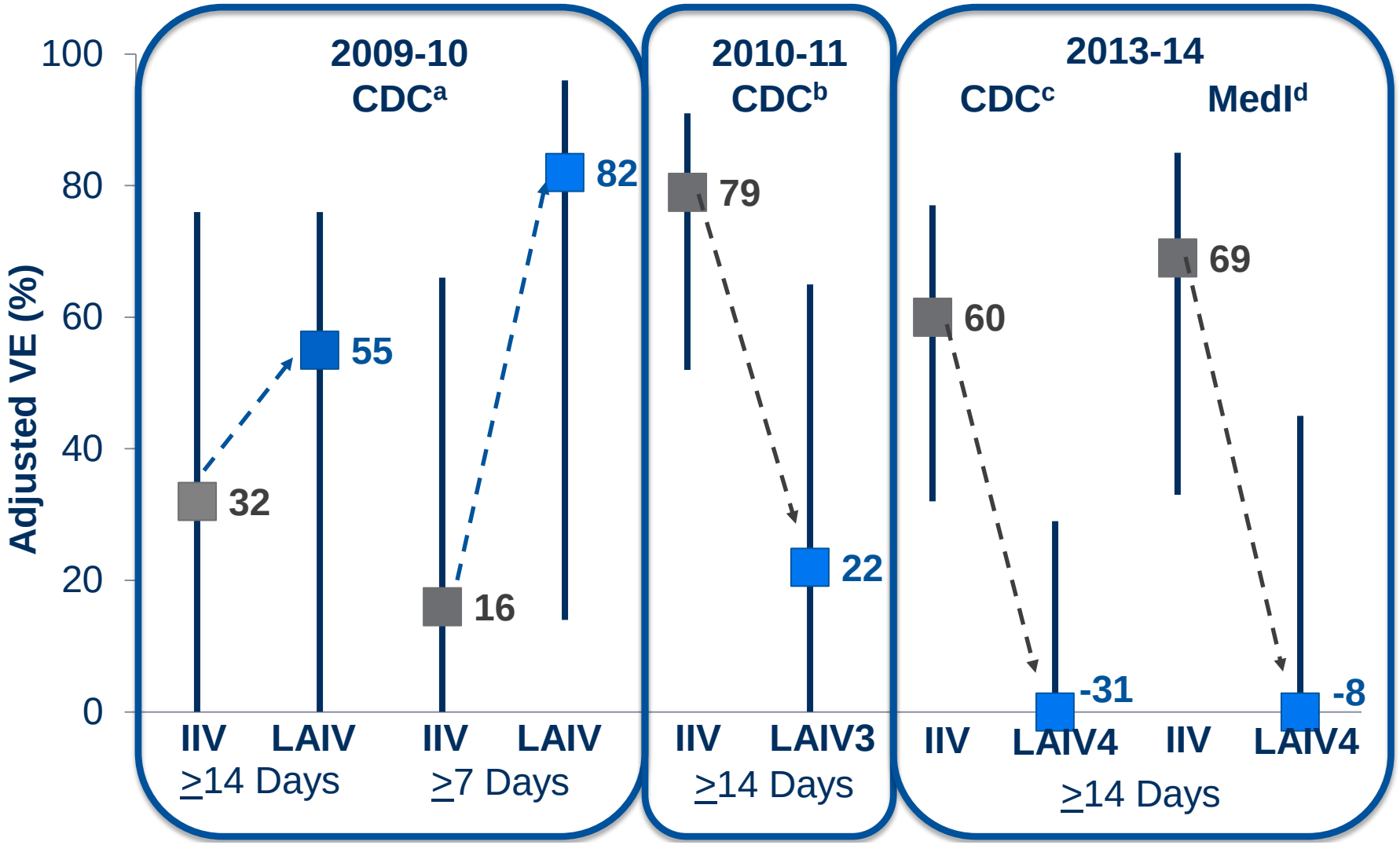
# US VE Against H3N2 and B in Children 2-8 Years




Data for children 2-8 years of age. Adjusted VE estimates are not controlled for differences between LAIV and IIV recipients. Studies did not have sufficient statistical power to demonstrate superiority.

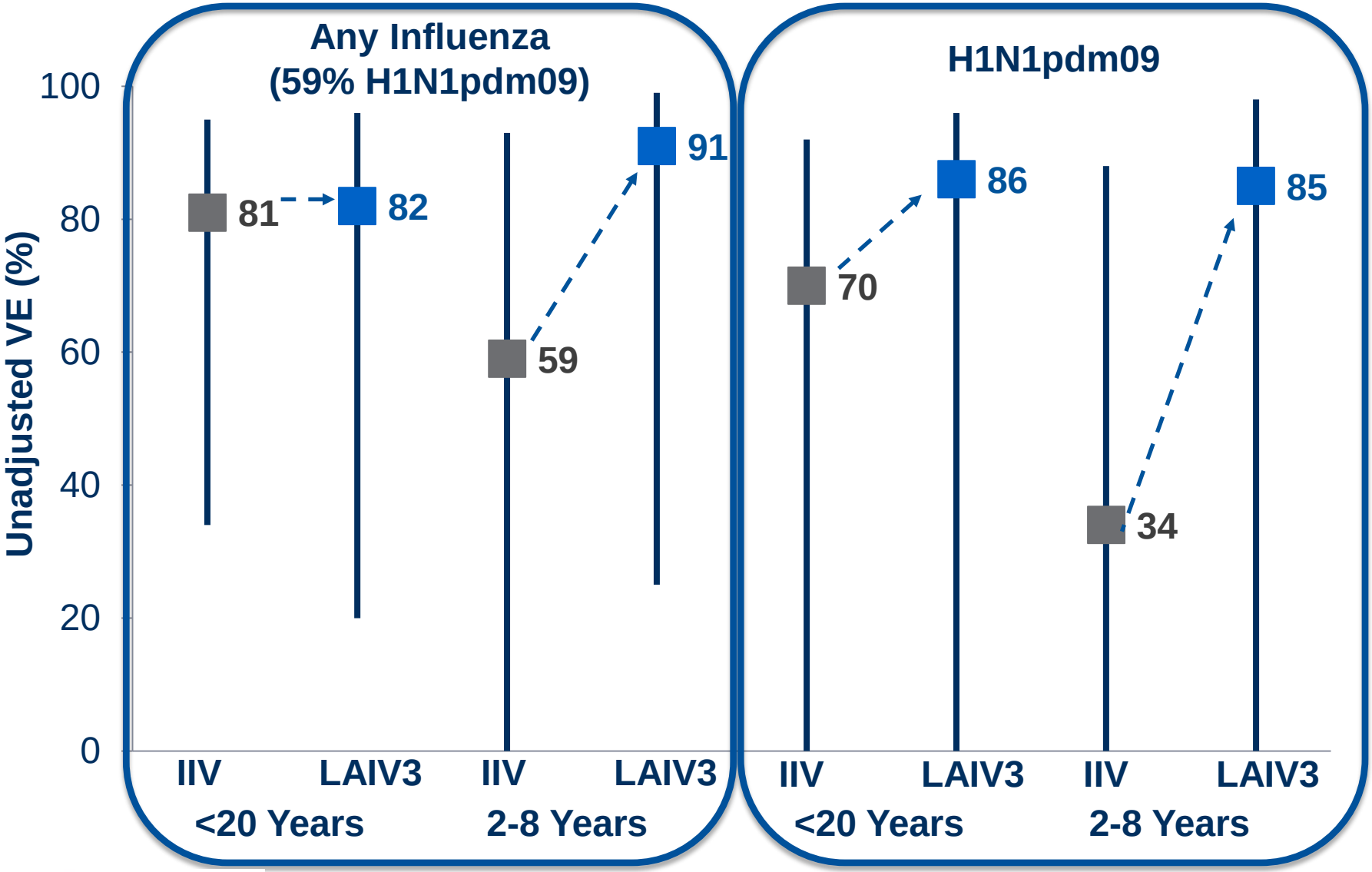
*H3N2 was predominant in 2011-12; H1N1pdm09 and B strains also co-circulated. In 2012-13 H3N2 was predominant early in the season and B was predominant late in the season.

# US VE Against H1N1pdm09 in Children <9 Years




[a] LAIV data for children 2-9 years of age and IIV data for children 6mo-9 years of age from Griffin, 2011. LAIV is not indicated for children under 24 months; [b] Data for children 2-8 years of age from CDC personal communication; [c, d] Data for children 2-8 years of age from CDC personal communication and MedImmune data on file. No data is available regarding effectiveness against H1N1pdm09 strains in 2011-12 or 2012-13 as H1N1 strains did not circulate to a meaningful degree during those seasons.

# Canadian VE Results from 2013-14

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*Unpublished SPSN data from personal communication with Dr. Skowronski. Effectiveness estimates were unadjusted due to limited sample size. Estimated that 59% of cases were A/H1N1pdm09, 6% A/H3N2, 35% B. Data for BC, Alberta, Quebec.

# Canadian RELATIVES Study Data for LAIV[1]

**(2013 - 2014 SEASON)**

- Cluster-randomized trial of LAIV and IIV in elementary school children in Ontario and their households
- Results indicate that LAIV provided protection against H1N1pdm09 strains
  - 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), $p<0.05$
- Results not consistent with lack of effectiveness of LAIV against H1N1pdm09 strains

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[1] Kwong J, et al., Abstract from the Canadian Immunization Conference, December 2014.

# 2 Hypothesis to Explain VE Results

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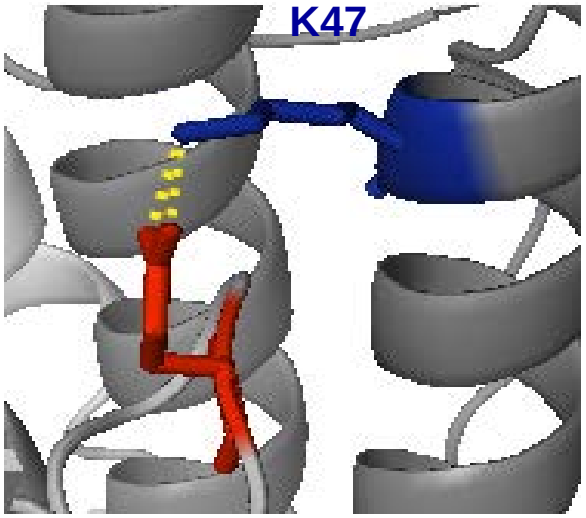
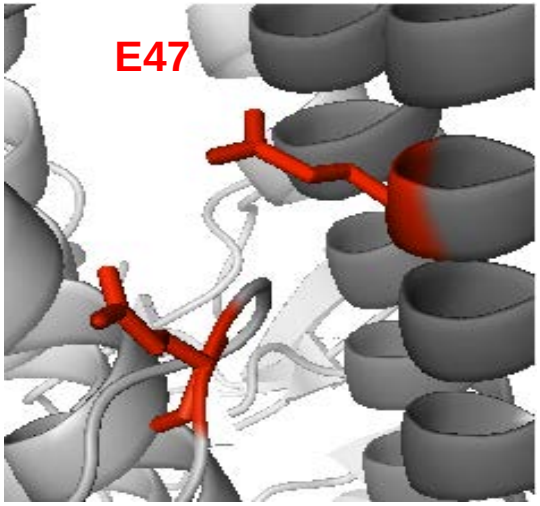
# Unique A/California HA Stalk Sequence

- A/California/7/2009 (H1N1pdm09) wild-type and LAIV contain E47 residue in HA stalk that reduces HA trimer stability and viral fitness[1]
- E47 is not present in seasonal viruses and is not prevalent in current H1N1pdm09 viruses




**Seasonal influenza viruses more stable**




**A/California H1N1pdm09 less stable**

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[1] Cotter, et al., 2014 :PLoS Pathogen 10(1): e1003831.

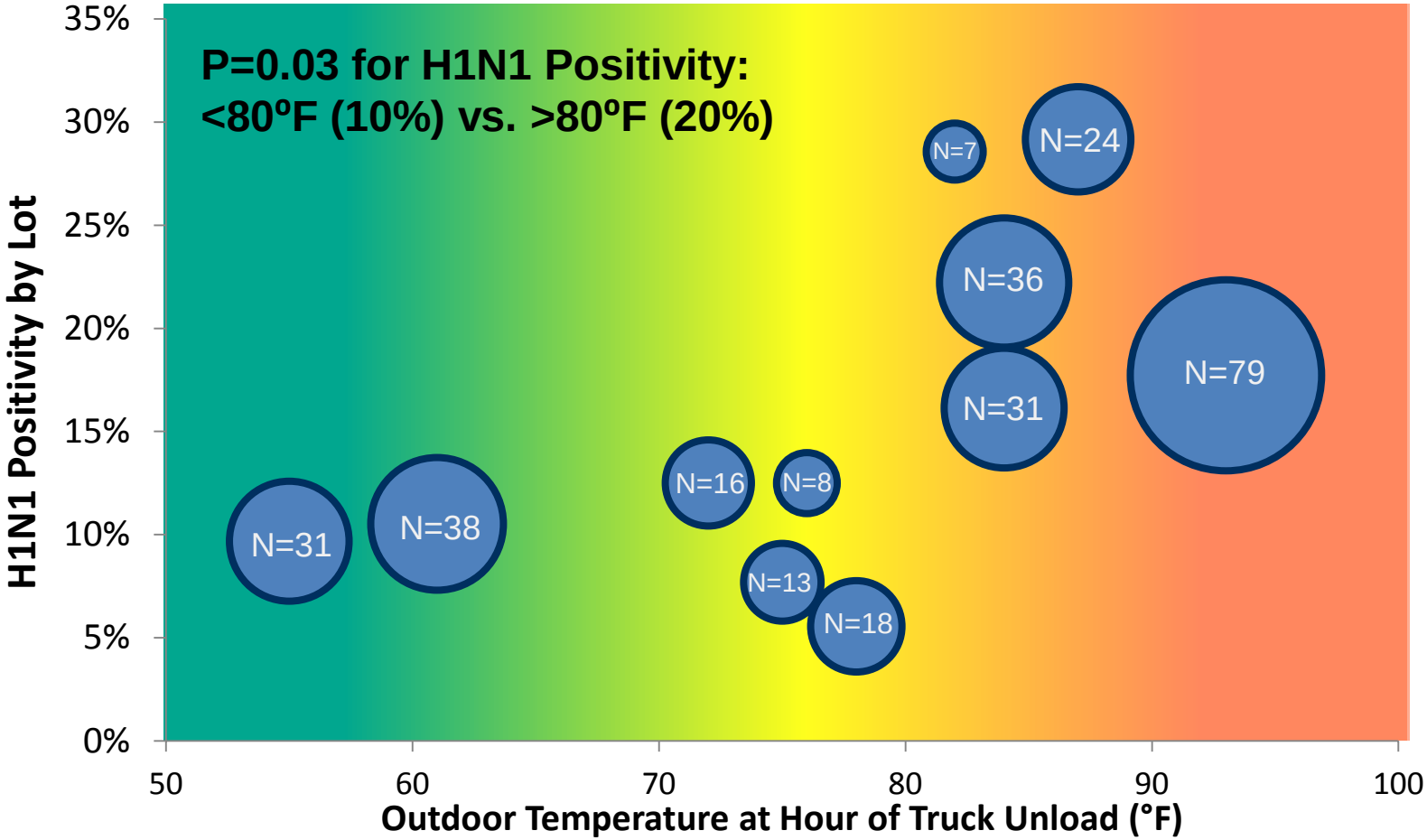
# HA Stalk Sequence E47 Reduces Virus Infectivity and Increases Vulnerability to Heat

- Reduces infectivity in ferrets
  - In two H1N1pdm09 viruses, E47 sequence (compared to K47) was linked to 5-fold reduced infectivity in ferrets
- Increases vulnerability to heat degradation
  - HA stability can be assessed in laboratory by measuring HA degradation at 120-160ºF
  - A/California/7/2009 LAIV strain with E47 sequence is readily differentiated from other seasonal Type A and B LAIV strains

# Normal US Vaccine Distribution Processes Entail Exposures to Temperatures >70°F

- No significant exposures above recommended temperatures occurred in MedImmune facilities or chain of control
- Exposures >36-46°F can occur at multiple subsequent points:
  - Receipt at distributors, packing out from distributors, unpacking and handling at clinic
- No data available on precise vaccine temperature during distribution
- Laboratory studies of A/California potency at 91ºF demonstrate 1-log potency drop by TCID50 at 24 hours
  - Evaluating the impact of multiple shorter-term exposures to 77-91ºF on longer-term potency and infectivity

# Outdoor Temperature at Truck Unloading Correlates with H1N1 Illness by Lot in LAIV recipients in 2013-14 Studies




Data for CDC and MedImmune studies are combined by lot/distributor. Circles represent individual lots; circle size is proportional to number of subjects receiving the lot. Lots used in ≤6 subjects were combined with lots experiencing most similar unloading temperatures. Lots shipped by refrigerated parcel (not by truck) were classified as being exposed to 55°F.

# Observed Effectiveness of A/California LAIV by Season Also Correlates with Shipping in Late Summer

| | Influenza Season/Study | | | | |
|---|---|---|---|---|---|
| | US 2009-10 CDC[a] | US 2010-11 CDC[b] | US 2013-14 CDC[c] | US 2013-14 MedI[d] | Canada 2013-14[e] |
| Estimated Proportion of LAIV Doses Shipped Before Mid-Sept | 0% | ~50% | 81% | 84% | 0% |
| VE Estimate for 2-9 year olds (95% CI) | 82% (14, 96) | 22% (-74, 65) | -31% (<0, 29) | -8% (-115, 45) | 85% (-22, 98) unadjusted |

[a] LAIV data for children 2-9 years of age from Griffin, 2011. VE listed is with 7 day exclusion window post vaccination; [b] Data for children 2-8 years of age from CDC personal communication; [c] Data for children 2-8 years of age from CDC presentation; [d] MedImmune data on file; [e] Unpublished data from personal communication with Dr. Danuta Skowronski. VE estimates were unadjusted due to limited sample size. All LAIV was shipped mid-October and later.

No data is available regarding effectiveness against H1N1pdm09 strains in 2011-12 or 2012-13 as H1N1 strains did not circulate to a meaningful degree during those seasons.

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# Reduced Fitness and Increased Vulnerability of A/California LAIV to Heat Degradation Can Explain VE Results

- A/California stalk sequence reduces viral fitness and makes strain more vulnerable to heat degradation
- Normal US vaccine shipping & handling entails exposures to >70°F
- Outdoor heat during shipping correlates with reduced VE of A/California LAIV
- At 1 log lower potency, LAIV efficacy was significantly reduced in a randomized, placebo-controlled efficacy study in children[1]
- Poor HA stability and vulnerability to heat exposure is unique to A/California LAIV
  - VE of all other LAIV strains evaluated in recent seasons was consistently moderate/high

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1. Forrest, et al., Clin Vaccine Immunol, 15:1042-1053, 2008

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# Plan of Action for 2015-16 and Future Influenza Seasons

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# Plan of Action for 2015-16 and Future Influenza Seasons

- Replace A/California LAIV with antigenically similar strain with more stable HA
- No future strains will possess the E47 residue
- Future strains will have heat tolerance similar to LAIV strains with demonstrated effectiveness
- Work with distributors to eliminate significant exposures to temperatures above 46ºF

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# Upcoming Effectiveness/Efficacy Data for Quadrivalent LAIV[1]

| Type of Study | Sponsor | Country | LAV Formulation | Timing |
|---|---|---|---|---|
| Effectiveness (Test-Negative, Case-Control) | CDC | USA | Quadrivalent | Annual |
| | MedImmune | USA[2] | Quadrivalent | 2013-14 to 2016-17[3] |
| | Public Health Agency of Canada | Canada | Quadrivalent | Annual |
| Effectiveness (Case-Control and Community-Level) | Public Health England | UK | Quadrivalent | Annual |
| Efficacy (Randomized Placebo-Controlled) | MedImmune | Japan[4] | Quadrivalent | 2015 |

[1] In 2014-15, LAIV4 was the only formulation currently used in US, EU, and Israel, and was predominant formulation used in Canada. Beginning in 2015-16 season, LAIV4 will be the only formulation available globally.
[2] Planning to expand in 2015-16 to include clinical sites in the UK.
[3] Study may extend beyond 2016-17.
[4] Children 6-18 years of age.

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