Update: Live Attenuated Influenza Vaccine (LAIV)

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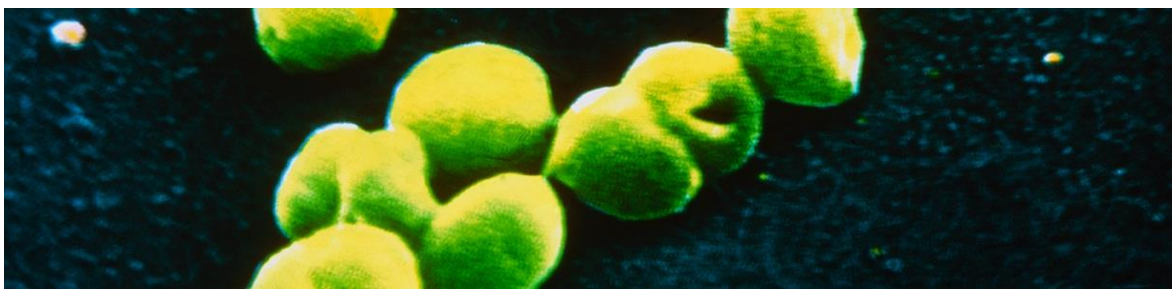
National Adult and Influenza Immunization Summit May 11, 2017



Conflict statement:

Allyn Bandell is an employee of AstraZeneca

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FluMist Quadrivalent

- In 2016, the ACIP issued an interim recommendation that FluMist Quadrivalent should not be used due to reduced effectiveness
- FluMist Quadrivalent (live attenuated influenza vaccine quadrivalent) remains an FDA-approved seasonal influenza vaccine and continues to be used in other countries (UK, Canada, EU)
- AstraZeneca believes that FluMist Quadrivalent is an important option for seasonal influenza vaccination and pandemic preparedness
- We have initiated a broad-based investigation into the causes of reduced effectiveness in recent seasons.
- Our findings to date have shown that A/H1N1pdm09 LAIV strains do not replicate as well as pre-pandemic A/H1N1 LAIV strains

ACIP, Advisory Committee on Immunization Practices; FDA, Food and Drug Administration

Observations of reduced LAIV effectiveness

- Evidence of reduced effectiveness is limited to outpatient H1N1pdm09 illness
  - Low to no VE with LAIV3 and LAIV4 in 2010–2014[1]
  - Reduced VE with LAIV4 in 2015–2016 against outpatient ILI in all countries[1]
  - Moderate VE with LAIV4 in 2015–2016 against hospitalized influenza in UK[2,3]

- No evidence of reduced effectiveness against matched A/H3N2 and B strains
  - Low VE observed in 2014–2015 against significantly mismatched A/H3N2, similar to IIV and previous randomized studies with LAIV[1]
  - Matched A/H3N2 VE for LAIV4 expected from 2016–2017 season[4]

IIV, inactivated influenza vaccine; ILI, influenza-like illness; VE, vaccine effectiveness

1. Caspard H et al. PAS 2017 poster presentation.
2. Pebody R et al. *Euro Surveill*. 2017;22(4):pii=30450.
3. Health Protection Scotland. Available at http://www.hps.scot.nhs.uk/resourcedocument.aspx?id=5529 [Accessed February 16, 2017].
4. CDC Weekly U.S. Influenza Surveillance Report. Available from https://www.cdc.gov/flu/weekly/index.htm#ILIMap [Accessed May 4, 2017].

New data: LAIV4 effectiveness against influenza hospitalization in 2015–2016 influenza season

	Vaccine effectiveness: percentage (95% CI)	
Endpoint	**Public Health England[1]**	**Health Protection Scotland[2]**
Lab-confirmed influenza due to any strain	**55% (32, 68)**	**63% (50, 72)**
Lab-confirmed influenza due to H1N1 pdm09 strains	**48% (17, 68)**	**NA**
Lab-confirmed influenza due to B strains	**71% (33, 87)**	**NA**
Clinical diagnosis of influenza	**NA**	**68% (42, 83)**

UK will continue to roll-out pediatric influenza vaccination program with LAIV to all 4–11-year-olds

LAIV4, quadrivalent LAIV

1. Peabody R et al. *Euro Surveill.* 2017; 22(4):pii=30450.
2. Health Protection Scotland. http://www.hps.scot.nhs.uk/resourcedocument.aspx?id=5529. Accessed February 16, 2017.

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Differences in US and EU childhood influenza vaccination practices

	US	Europe
Influenza vaccine recommendations	• Recommended for all ≥6 months without contraindications[1] • LAIV4 not recommended for 2016–2017 season[1]	• A **minority** of countries recommend childhood influenza vaccination[2] • **UK and Finland** have childhood vaccination programs with LAIV[3,4]
Vaccination coverage: 2015–2016	• Children aged 6 months to 17 years: **59.3%[5]**	• UK, children 2–<5 years[6]: **32%** • Finland, children 24–35 months*: **22%**[4] • Generally low coverage in other countries[2]

*Age groups recommended for vaccination in 2015–2016 season; †Information correct as of 2016

1. Grohskopf LA et al. *MMWR Recomm Rep.* 2016;65(5):1–54. 2. McGuire A et al. *Expert Rev Vaccines.* 2016;15(5):659–670. 3. Kassianos G et al. *Drugs Context.* 2015;4:212280.
4. Nohynek H et al. *Euro Surveill.* 2016;21(38):30346. 5. CDC Flu Vaccination Coverage. Available at https://www.cdc.gov/flu/fluvaxview/coverage-1516estimates.htm [Accessed April 25, 2017].
6. Public Health England Influenza immunisation programme for England. Available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/544552/Seasonal_flu_GP_patient_groups_annual_report_2015_2016.pdf [Accessed May 4, 2017].

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LAIV effectiveness investigation: Root causes

- **Most likely root cause: reduced replicative fitness of H1N1pdm09 LAIV strains**
- Potential contributing factor: vaccine virus interference in LAIV3 and LAIV4
- No support for the following as likely root causes
  - Pre-existing immunity from prior vaccination
  - Quadrivalent-specific vaccine virus interference
  - Vaccine virus temperature stability and heat exposure during shipping
  - Vaccine virus development
  - Manufacturing
  - Stability at 2–8° C

7 Internal Da Status of investigation of reduced LAIV effectiveness. MedImmune, Gaithersburg, MD. October 2016

Unlikely root cause: Pre-existing immunity among vaccinated children

- **No evidence of reduced LAIV effectiveness in children with prior vaccination**
  - No evidence from LAIV development in multiple randomized studies
  - No evidence of decrease in VE against B strains in observational studies since 2010–2011
  - Reduced H1N1pdm09 VE has not correlated with prior vaccination in any study[1–3]
- **Available LAIV H1N1pdm09 VE estimates trended higher among previously vaccinated versus not previously vaccinated**
  - MedImmune US study: 19% versus 9% (2013–2014); 60% versus 35% (2015–2016)[2]
  - Finland: 74% versus 25% (2015–2016)[1]
- **Given these observations, pre-existing immunity considered unlikely root cause of the reduced VE**
- **Additional matched H3N2 data should be available from Japan efficacy study in subjects 2–18 years of age during the 2016–2017 season**

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1. Nohynek H et al. *Euro Surveill*. 2016;21(38):pii=30346.
2. Internal data. Status of investigation of reduced LAIV effectiveness. MedImmune, Gaithersburg, MD. October, 2016.
3. CDC Flu VE Network results, presented at ACIP

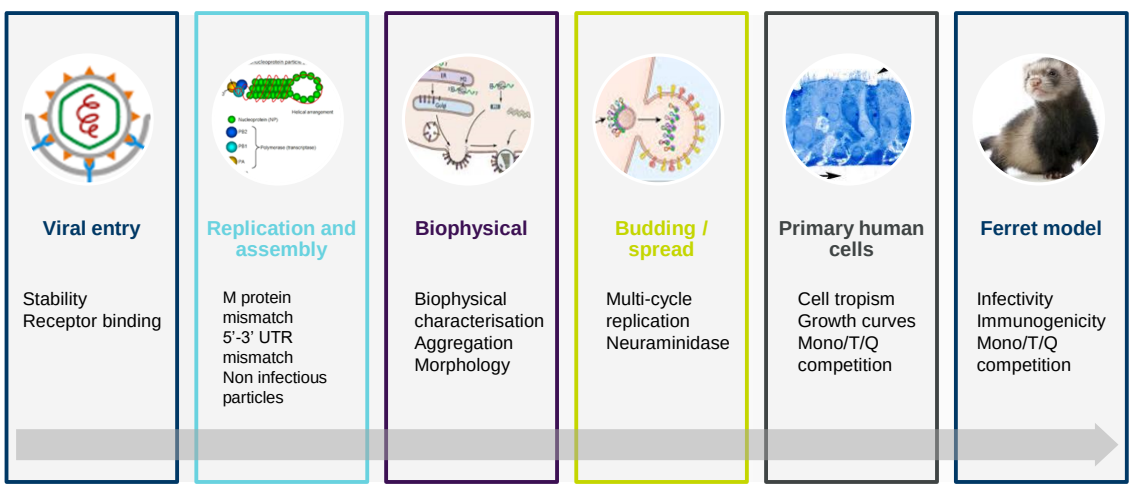
Unlikely root cause: Vaccine virus interference from quadrivalent formulation

- **Reduced VE observed with LAIV3 and LAIV4**
  - LAIV3 demonstrated low to no VE against H1N1pdm09 strains in 2010–2011[1,2]
  - 0% (95% CI: –26, 21) A/H1N1pdm09 efficacy with A/Leningrad LAIV3 in a randomized, placebo-controlled study in children in Senegal[3]

- **Given these observations, quadrivalent-specific interference considered unlikely root cause of the reduced VE**
- **However, interference could be a contributing factor to the low VE in context of reduced replicative fitness of A/H1N1pdm09 LAIV strains**

1. Chung JR et al. *Pediatrics.* 2016;137(2):e20153279.
2. Helmeke C et al. *PLoS One*. 2015;10(4):e0122910.
3. Victor JC et. al. *Lancet Glob Health.* 2016;4(12):e955–e965.

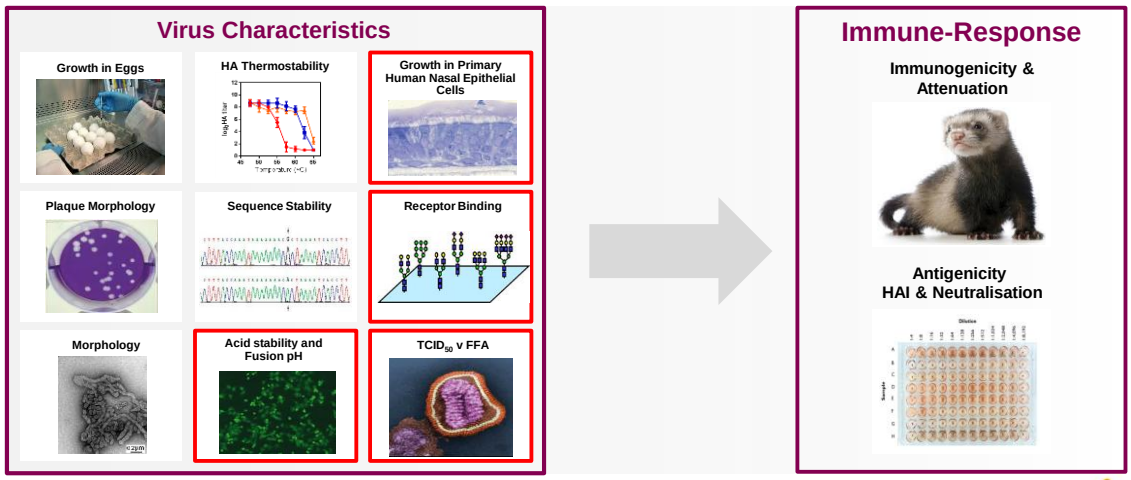
Reduced replicative fitness: Virus life-cycle focused



Pre-2009 H1N1
- **A/New Caledonia/20/99 (NC99)**
- **A/South Dakota/06/07 (SD07)**

H1N1 pdm09
- **A/California/07/09 (CA09)**
- **A/Bolivia/559/13 (BOL13)**
- **A/Slovenia/2903/2015 (SLO15)**

New characterization assays introduced into strain selection process



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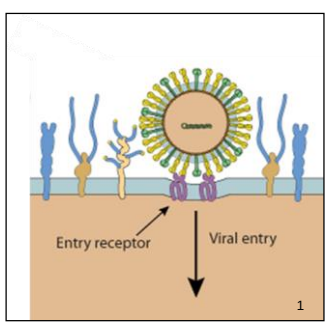
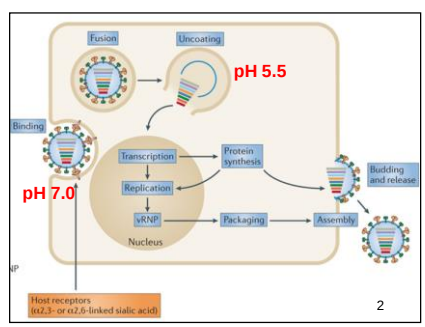
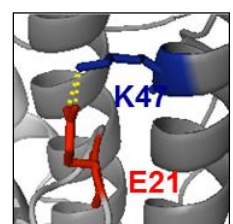
Characteristics of A/Slovenia (2017–18 H1N1pdm09 strain)

Improved receptor binding compared to A/Bolivia	Activation pH improved compared to A/Bolivia	More heat stable compared to A/California







K47 More Stable

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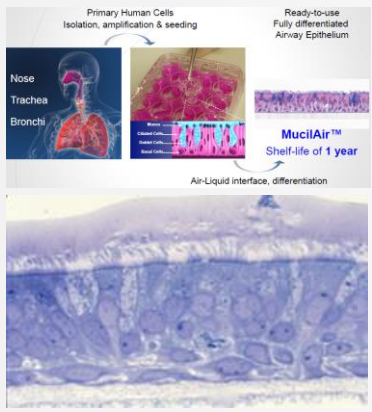
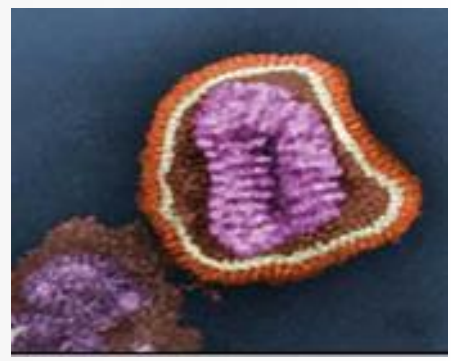
1. Modified from Swiss Institute of Bioinformatics. Available at http://viralzone.expasy.org/. 2. Shi Y et al. Nat Rev Microbiol. 2014 Dec;12(12):822-31.

Improved replication in human nasal epithelium compared to A/Bolivia



No deficit with replication over multiple cycles



Internal Dara. Status of investigation of reduced LAIV effectiveness. MedImmune, Gaithersburg, MD. February 2017.

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Pediatric Study:
2017–18 LAIV4 with A/Slovenia compared to LAIV formulations with A/Bolivia

Objective: Differences in immunogenicity and shedding between A/Slovenia and A/Bolivia strains

Design:

- Randomized, double-blind
- Enroll ~200 children 24 to <48 months
- Subjects randomized (~65 per group) at 1:1:1 ratio to receive two doses of:
  - LAIV4 2017-2018 (A/H1N1 Slovenia strain)
  - LAIV4 2015-2016 (A/H1N1 Bolivia strain)
  - LAIV3 2015-2016 (A/H1N1 Bolivia strain)

Primary endpoint:

- HAI antibody seroconversion rates after each dose

Secondary endpoints:

- Neutralizing antibody seroconversion rates after each dose
- Mucosal IgA increases after each dose
- Shedding after each dose
- Safety

Internal data. Draft study protocol. Medimmune, Gaithersburg, MD. April 2017.

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Data availability

Available to-date

- 2010–2016 VE meta-analysis
- 2015–2016 VE hospitalized flu
- Early A/Slovenia laboratory characterization

June 2017

- Additional A/Slovenia laboratory characterization
- 2016–2017 VE data: UK, Finland, Canada

October 2017

- Shedding/immunogenicity study of A/Slovenia vs A/Bolivia in US Children
- Japan 2016–18 Paediatric efficacy study data (H3N2, B)

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Conclusions

- Reduced LAIV effectiveness is limited to H1N1pdm09 illness in outpatient setting
- Significant investigations are ongoing and have revealed the following:
  - Most likely root cause: reduced replicative fitness of H1N1pdm09 LAIV strains
  - Potential contributing factor: vaccine virus interference
- New assays used to select A/Slovenia strain for 2017–2018, which demonstrates improved viral fitness
- Planned clinical study will assess A/Slovenia strain in US children, data expected October 2017
- Additional data regarding 2016–17 effectiveness expected in months ahead

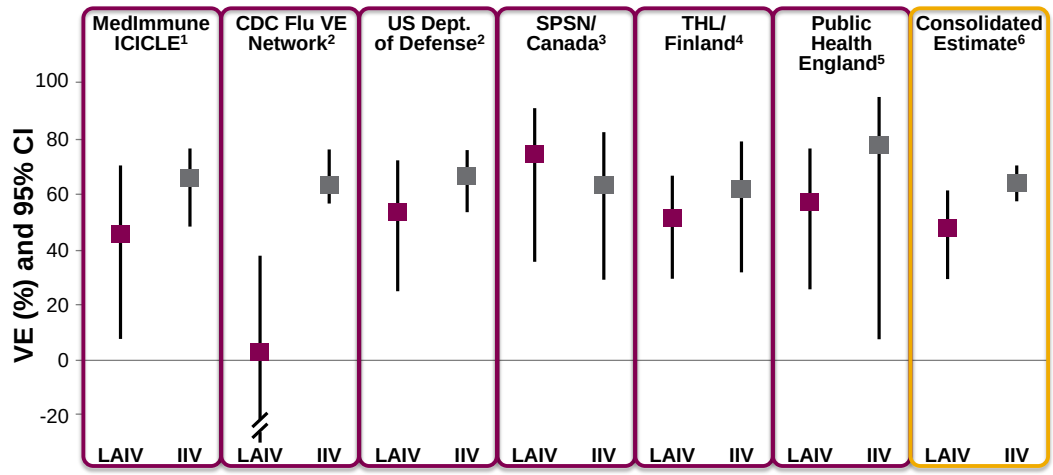
AstraZeneca/MedImmune remains committed to FluMist Quadrivalent as an important option for seasonal influenza vaccination and pandemic preparedness

16 MedImmune Presentation to ACIP. Atlanta, GE. February 22, 2017. Internal data.. Status of investigation of reduced LAIV effectiveness. MedImmune, Gaithersburg, MD, 2016.

Thank you

Back up slides

LAIV and IIV effectiveness estimates for all strains: 2015–2016 influenza season



Lower bound of CIs was truncated at –30.

1. Ambrose C. Presented at Advisory Committee on Immunization Practices Meeting; June 22, 2016; Atlanta, GA 2. Flannery B. Presented at Advisory Committee on Immunization Practices Meeting; June 22, 2016; Atlanta, GA 3. Caspard H et al. Presented at International Society for Influenza and Other Respiratory Virus Diseases (ISIRV) Options IX for the Control of Influenza Conference; August 25, 2016; Chicago, IL. 4. Nohynek H et al. *Euro Surveill.* 2016;21(38):pii=30346. 5. Pebody R et al. *Euro Surveill.* 2016;21(38):pii=30348. 6. Caspard H. Abstract Accepted for Publication PAS, May 6-9, 2017; San Francisco, CA.

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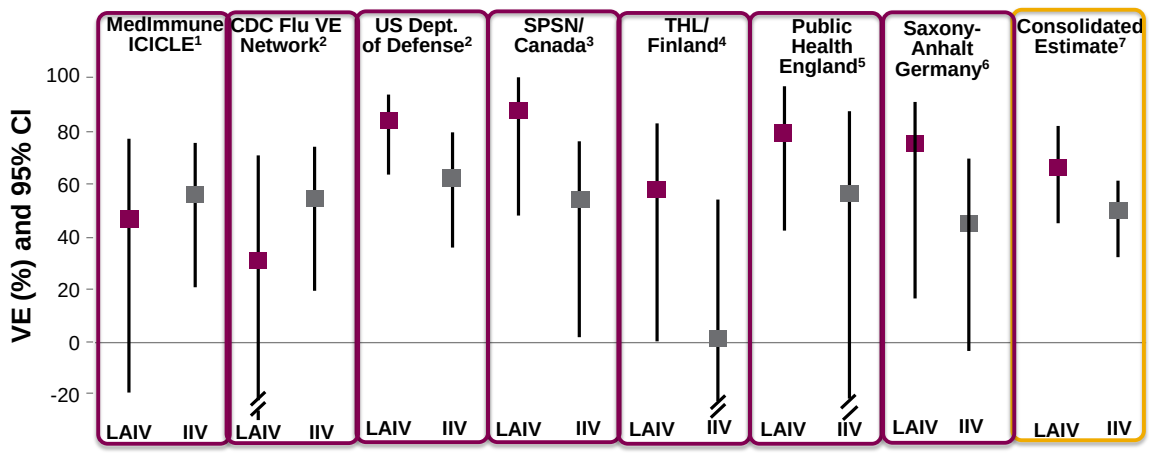
LAIV and IIV effectiveness estimates for B Strains: 2015–2016 influenza season



Lower bound of CIs was truncated at –30.

1. Ambrose C. Presented at Advisory Committee on Immunization Practices Meeting; June 22, 2016; Atlanta, GA 2. Flannery B. Presented at Advisory Committee on Immunization Practices Meeting; June 22, 2016; Atlanta, GA 3. Caspard H et al. Presented at International Society for Influenza and Other Respiratory Virus Diseases (ISIRV) Options IX for the Control of Influenza Conference; August 25, 2016; Chicago, IL. 4. Nohynek H et al. *Euro Surveill.* 2016;21(38):pii=30346. 5. Pebody R et al. *Euro Surveill.* 2016;21(38):pii=30348. 6. Helmeke C et al. http://www.verbraucherschutz.sachsen-anhalt.de/fileadmin/Bibliothek/Politik_und_Verwaltung/MS/LAV_Verbraucherschutz/hygiene/influenza/Effektivitaet_der_Influenzaimpfstoffe_2015-16.pdf 7.Caspard H. Abstract Accepted for Publication PAS, May 6-9, 2017; San Francisco, CA.

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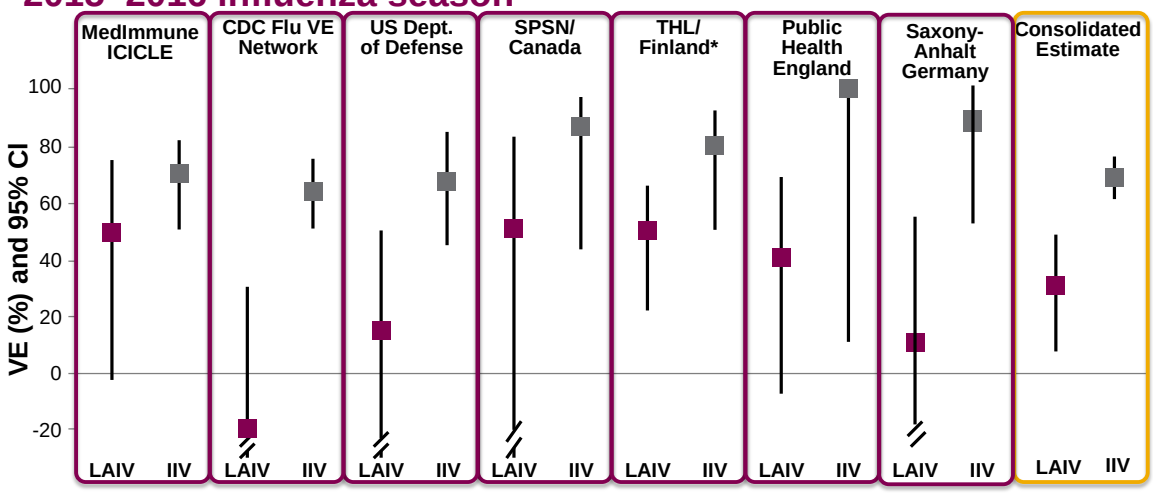
LAIV and IIV effectiveness estimates for A/H1N1pdm09 strains: 2015–2016 influenza season[1,2]



Lower bound of CIs was truncated at –30.* Effectiveness estimate against any A strain.

1. Caspard H et al. Abstract accepted for presentation at: Pediatric Academic Societies Meeting; May 6-9, 2017; San Francisco, CA.
2. Helmeke C et al. [poster]. Presented at: European Scientific Conference on Applied Infectious Disease Epidemiology; Nov 28-30, 2016; Stockholm, Sweden.

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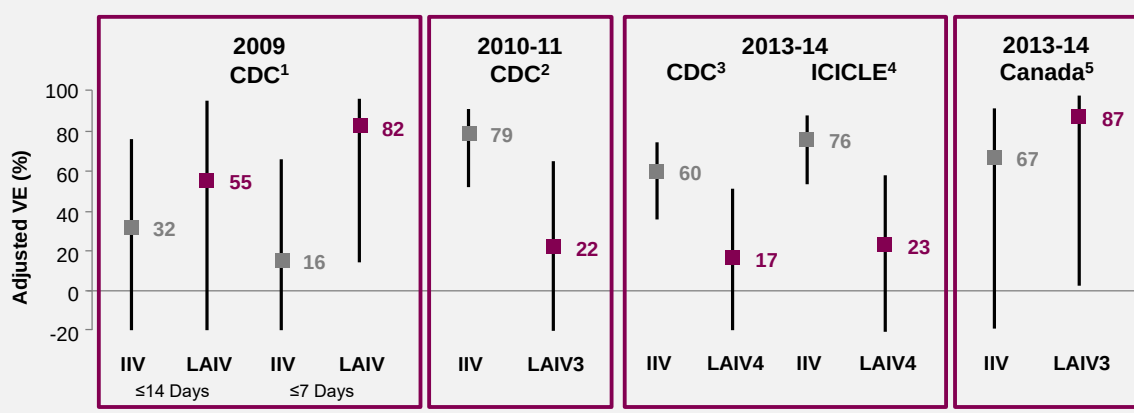
2009–2014 VE of IIV and LAIV against H1N1pdm09 in children



1. LAIV data for children 2–9 years of age and IIV data for children 6 mo–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 years 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.

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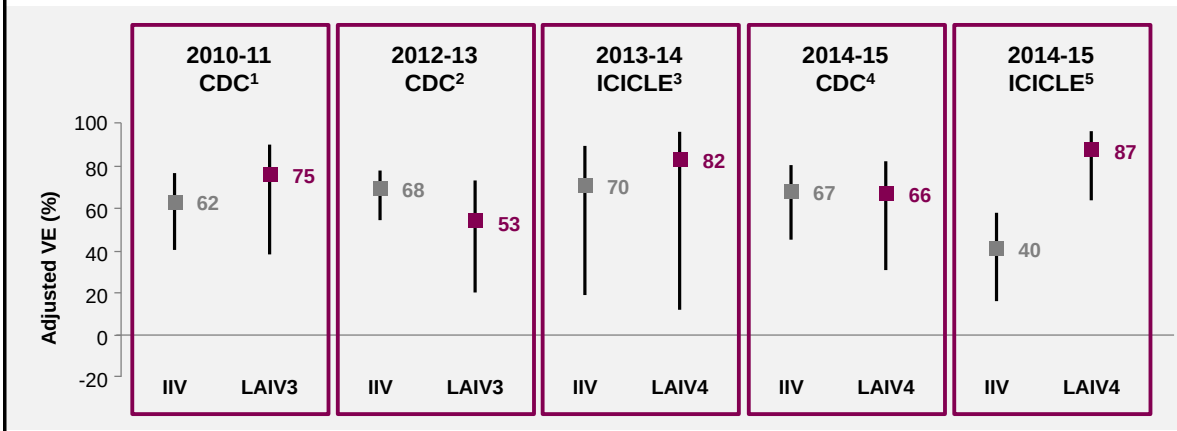
2010–2015 VE of IIV and LAIV against Influenza B in children



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.

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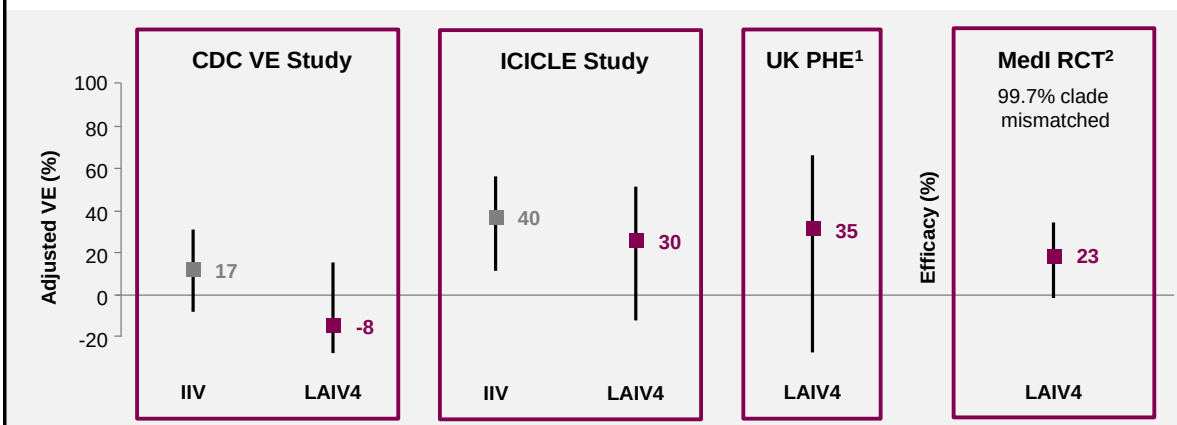
2014–15 A/H3N2 VE of LAIV and IIV in children



CDC data based on most recent ACIP presentation. ICICLE estimate based on pending publication. 1. Pebody et al. *Euro Surveill.* 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.

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Current recommendations for LAIV: 2016–2017 season

Population	Country	Age range	Recommendation
Healthy* children	US[1]	≥6 months	Recommendation for vaccination with IIV LAIV not recommended for use in 2016–2017 season
Healthy* children	Canada[2]	≥6 months 2–17 years	Recommendation for vaccination LAIV approved for use, no preferential recommendation
Healthy* children	UK[3]	2–17 years	LAIV should be vaccine of choice
Healthy* children	Israel[4]	6 months to 2 years 2–17 years	Recommendation for vaccination with IIV LAIV available but preferential recommendation for IIV
At-risk children	Germany[5]	2–17 years	IIV or LAIV Preferential recommendation for LAIV in children aged 2–6 years suspended in 2016–2017 season
At-risk children	Norway[7,8]	6 months to 2 years 2–17 years	IIV only LAIV approved for use, no preferential recommendation
Healthy* children	Finland[9]	6–<24 months and >35 months 24–35 months	Preferential recommendation for IIV (Influvac) Preferential recommendation for LAIV4

*Healthy children - according to the licensed indications and excludes contraindicated and special precautionary groups.
IIV, Inactivated influenza vaccine; LAIV, live attenuated influenza vaccine (Q/LAIV, quadrivalent LAIV).
LAIV, Live attenuated influenza vaccine; IIV, traditional injectable vaccine; WHO, World Health Organisation. 1. Grohskopf LA et al. MMWR Recomm Rep 2016;65(No. RR-5):1–54. 2. NACI statement on seasonal influenza vaccine. Available at http://www.phac-aspc.gc.ca/naci-ccni/flu-2016-grippe-eng.php [Accessed 26 April 2017]. 3. JCVI minutes, Positioning statement on the annual influenza vaccination program. Published 25 July 2012 at: http://transparency.dh.gov.uk/2012/07/25/jcvi-meeting-june-2012/. [Accessed 25 April 2017]. 4. Israel ministry of health: http://www.health.gov.il/English/Topics/Pregnancy/Vaccination_of_infants/Pages/flu_children.aspx . [Accessed 25 April 2017]. 5. STIKO Epidemiologisches Bulletin No. 34. Available at http://www.rki.de/EN/Content/infections/Vaccination/recommandations/34_2016_engl.pdf?__blob=publicationFile [Accessed 25 April 2017]. 7. Norway influenza prevention. Available at: https://www.fhi.no/en/id/influensa/seasonal-influenza/influenza_advice/advice-about-influenza-prevention-a/ [Accessed 25 April 2017]. 8. Norway seasonal influenza vaccine. Available at https://www.fhi.no/en/id/influensa/seasonal-influenza/about-the-seasonal-influenza-vaccin/ [Accessed 25 April 2017]. 9. Finland influenza vaccination. Available at http://www.fimea.fi/web/en/for_public/influenza/influenza-vaccinations. [Accessed 25 April 2017].

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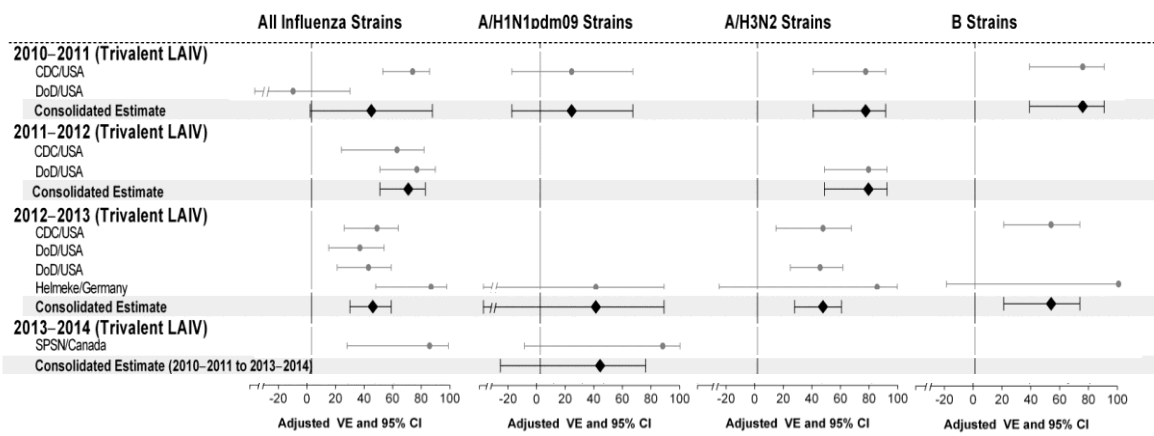
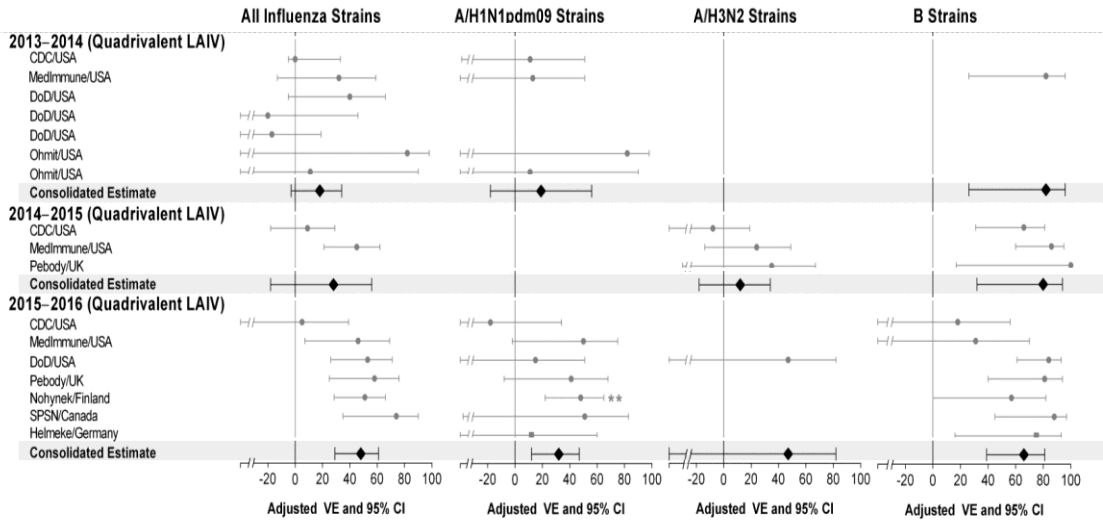
Meta-analysis: 2010-2014 trivalent LAIV effectiveness



*LAIV VE was 82% (95% CI, 14, 96) if children were censored when they had received LAIV <7 days before nasal swab, instead of <14 days.

26 Internal data. MedImmune. Gaithersburg, MD, Feb 2017.

Meta-analysis: 2013-2016 quadrivalent LAIV effectiveness



27 Internal data. MedImmune. Gaithersburg, MD, Feb 2017.