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Assessing Fever Rates in Children ages 24 to 59 months after Live Attenuated Influenza Vaccine (LAIV) or Inactivated Influenza Vaccine (IIV) During the 2013-14 Influenza Season

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Clinicaltrials.gov: NCT01764269

Disclaimers and Disclosures

The findings in this presentation are preliminary, data analysis is ongoing

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of CDC.

Disclosure:	Organization
Melissa Stockwell: Co-I (no financial support) Investigator-initiated study regarding vaccination of adolescents with chronic medical illness	Pfizer Medical Education Group

Fever LAIV/IIV Study: Background

- Live attenuated influenza vaccine (LAIV) potentially more effective than inactivated influenza vaccine (IIV) in children

- Characterizing fever rates after LAIV and IIV (with or without simultaneous vaccination) may help inform national policies for pediatric influenza vaccination
  - Including evaluation of quadrivalent influenza vaccines as they are introduced

Fever LAIV/IIV Study: Fever After LAIV vs. IIV

- One study in children suggested higher fever rate day 0-10 after LAIV vs. IIV, particularly day 2 (5.4% vs. 2.0%) (Belshe *et al* N Engl J Med. 2007)
  - Risk interval for fever after IIV is vaccination day and the day after vaccination (d0-1) (Rowhani-Rahbar *et al* Vaccine. 2012)

Fever LAIV/IIV Study: Text Messaging

- Text messaging can be used for public health surveillance and prevention efforts, such as reminder recalls for vaccination
- Successfully used text messaging to assess rates of fever after simultaneous vaccination with IIV3 and 13-valent pneumococcal conjugate vaccine (PCV-13) (Stockwell, Broder *et al* JAMA Pediatr. 2014)

Fever LAIV/IIV Study: Primary Objective

To assess the rates of fever in 24-59 month old children receiving LAIV compared to those receiving IIV.

***Primary Hypothesis*:** *Fever rates in risk window d0-2* post-vaccination will be higher in those receiving LAIV vs. IIV (D0-2: vaccination day, first 2 days post-vaccination)*

***Secondary Hypothesis**: Fever rates in the non-risk window d3-10 post-vaccination will not be significantly different in those receiving LAIV vs. IIV*

**risk window selected based on risk windows for IIV d0-1, LAIV d0-2*

Belshe et al N Engl J Med. 2007; Rowhani-Rahbar *et al* Vaccine. 2012

Fever LAIV/IIV Study: Secondary Objectives

- To assess whether fever rates in d0-2 post-vaccination are higher in those children receiving IIV4 vs. IIV3

- To characterize the clinical importance of the reported fevers with respect to height of the fever, occurrences of medically attended fever, and associated medically attended health outcomes

- *To explore whether fever rates after vaccination are different in children who receive LAIV simultaneously with other childhood vaccines vs. LAIV alone*

Fever LAIV/IIV Study: Study Design, Setting

- Observational prospective cohort study
  - Enrollment: September 13, 2013 – April 13, 2014
- Recruited from Columbia University Medical Center (CUMC)/ NewYork-Presbyterian Hospital clinical sites at vaccination
  - Vaccination decisions made solely by health care provider caring for the patient
  - Receipt of other vaccines was NOT an exclusion criterion
  - Approved by CUMC Institutional Review Board (CDC relied on the CUMC IRB)
- Consented and completed intake form; enrolled via text message; trained in use of temporal artery scanner thermometer

Fever LAIV/IIV Study: Study Population – Eligibility Criteria

Eligible study participants:

(1) are 24 through 59 months of age

(2) have a visit at a study site anytime during the study period

(3) receive first dose LAIV or IIV in the season

(4) the parent has a cell phone with text messaging capabilities

(5) the parent speaks English or Spanish

Fever LAIV/IIV Study: Exclusion Criteria

(1) chronic medical condition considered a contraindication or precaution to LAIV (except for asthma/wheezing history)

(2) currently on oral or other systemic steroids or used in past month

(3) currently on inhaled steroids or used in the past 2 weeks

(4) presence of fever ≥100.4˚F at time of vaccination

(5) administration of any antipyretic in the 6-hour period prior to vaccination

(6) stated intent, at time of vaccination, to use prophylactic antipyretics before the development of a fever

(7) parent only speaks a language other than English or Spanish

(8) parent's inability to read text messages

(9) child receiving the second dose of influenza vaccine in the current season

Fever LAIV/IIV Study: Text Messages

- d0 (day of enrollment): text message sent at 8pm
- d1-d10: text message sent at 8pm each night
- Information collected
  - Temperature range, actual temperature, time taken
  - Antipyretic medicine given, name and time
  - *Care sought (i.e. clinic and emergency department)*

Fever LAIV/IIV Study: Text Message Example

FeverFLU. Reply 1-5. Child's highest temperature since last text?

1 = 95.0 to 100.3

2 = 100.4 to 102.2

3 = 102.3 to 104.0

4 = above 104

5 = Did not take temp today

Fever LAIV/IIV Study: Daily Review of Text Responses

- Identification of non-responders
  - Initiate phone contact
  - Troubleshoot problems
  - Collect unreported temperatures

- Families also used paper diary and asked to send back at end of 10 days

Fever LAIV/IIV Study: Chart Abstraction

- Medically attended visits d0-10 (ambulatory care, emergency department and hospital) at NYP/CUMC
  - Chief complaint, final diagnosis
  - Review of symptoms
  - Documented temperatures

- Verify other vaccines (single and combination) given at time of enrollment using NewYork-Presbyterian Hospital's electronic health record, which includes an immunization registry (EzVac)

Fever LAIV/IIV Study: Analysis and Case Definitions

Days:

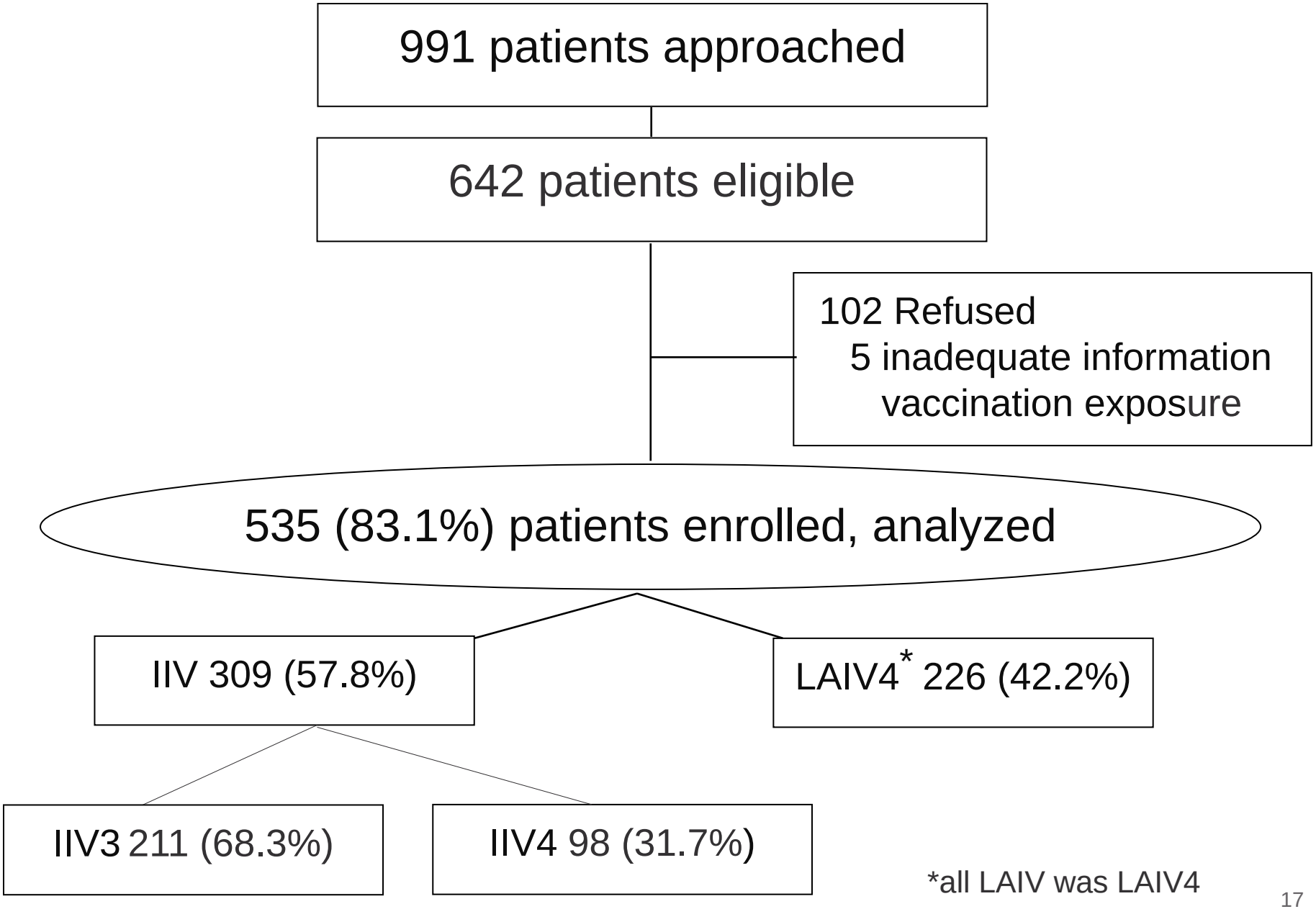
- Day 0: From immediately after vaccination to response to text sent at 8pm on vaccination day
- Day 1-10: From response to text sent at 8pm night before to response to text sent that night at 8pm

Fever

- Any: T $\geq$100.4˚F
- Moderate: T $\geq$102.2˚F

Periods: d0-2, d3-10

Fever LAIV/IIV Study: Study Flow Diagram



*all LAIV was LAIV4

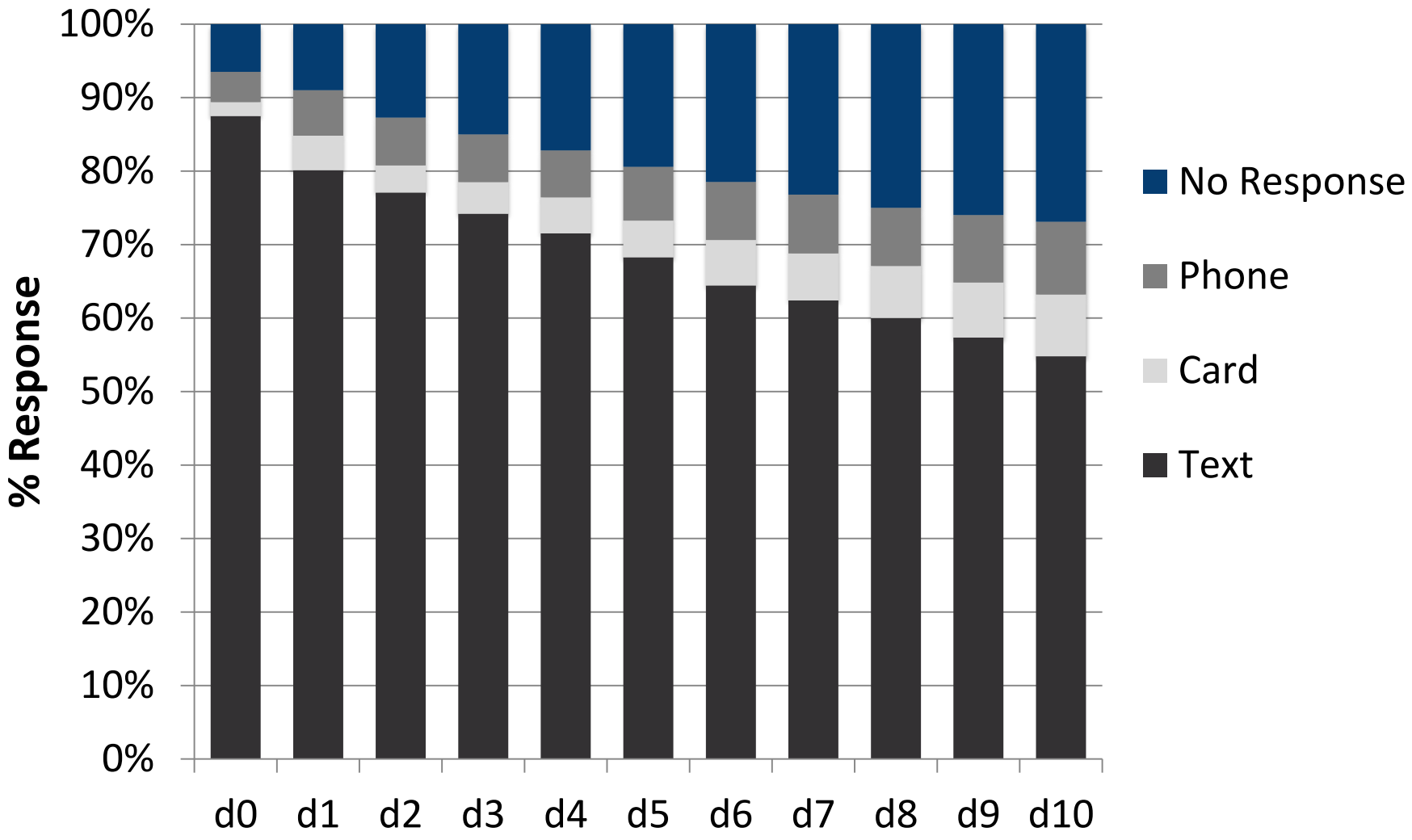
Fever LAIV/IIV Study: Age of Enrollees

N= 535	24-35 months	36-47 months	48-59 months
IIV3 (n=211)	130 (61.6%)	45 (21.3%)	36 (17.1%)
IIV4 (n=98)	0*	40 (40.8%)	58 (59.2%)
LAIV4 (n=226)	54 (23.9%)	85 (37.6%)	87 (38.5%)

Age distribution by vaccine: Pearson's Chi square: P <0.0001

* IIV4 formulation for <3 year olds not available at study sites

Fever LAIV/IIV Study: Information From All Sources



Fever LAIV/IIV Study: Fever Rates During Risk Window D0-2: T ≥100.4˚F

	Vaccine			
	IIV3 (n=174)	IIV4 (n=85)	LAIV4 (n=182)	Chi square P-value
% Fever	5.8% (n=15)		3.8% (n=7)	0.36
% Fever	5.2% (n=9)	7.1% (n=6)	3.8% (n=7)	0.53

NOTE: 4 of 22 fevers were T ≥102.2˚F; 0 in LAIV4

Fever LAIV/IIV Study: Fever Rates During Non-Risk Window D3-10: T ≥100.4˚F

Report all days (N=326)	Vaccine			
	IIV3 (n= 127)	IIV4 (n=64)	LAIV4 (n=135)	Chi square P-value
% Fever	9.9% (n=19)		10.4% (n=14)	0.90
% Fever	11.8% (n=15)	6.3% (n=4)	10.4% (n=14)	0.48

NOTE: 10 of 33 fevers were T ≥102.2˚F; 6 in LAIV4

Fever LAIV/IIV Study: Co-Administered Vaccines

Vaccine type (N=535)	Total (%)	IIV3 (%)	IIV4 (%)	LAIV4 (%)
Influenza alone (no other vaccine)	**62.4**	60.7	62.2	64.2
Influenza, (DTaP-IPV)*, MMRV	**13.3**	7.1	17.3	17.3
Influenza, HepA	**9.9**	16.6	2.0	7.1
Influenza, (DTaP-IPV)*, MMR, Varicella	**1.7**	0.5	7.1	0.4
Influenza, (DTaP-IPV)*, MMR	**1.7**	0.9	3.1	1.8
Influenza, MMR	**2.2**	4.3	0	1.3
Influenza, MMRV	**1.9**	1.4	3.1	1.8

*Kinrix® (DTaP-IPV)

- Combinations not shown represent <1%
- 82.6% with co-administered vaccine received DTaP-IPV and/or Hep A

Fever LAIV/IIV Study: Regression Model Risk Window D0-2: T ≥100.4˚F

- Log binomial regression adjusted for: *a priori*:
  - Hepatitis A vaccine, Kinrix® (DTaP-IPV) (most common inactivated vaccines administered)
  - Concurrent PCV13 vaccination (historical association)
  - Age group (12-23, 24-35, 36-48 months)
  - Previous receipt of influenza vaccination

- Other variables considered but not included based on non-significant (p-value >0.1) bivariate association with T ≥100.4˚F:
  - Ethnicity, gender, enrollment month, high risk for influenza

Fever LAIV/IIV Study: Regression Model During Risk Window D0-2: T ≥100.4˚F

	Frequency	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
IIV (n= 259)	5.8%	Ref	Ref
LAIV (n= 182)	3.8%	0.66 (0.28, 1.60)	0.60 (0.25, 1.45)

RR: Relative Risk; CI: Confidence Interval

Fever LAIV/IIV Study: Sensitivity Analyses- Risk Window D0-2: T ≥100.4˚F

Analysis Type	Frequency	aRR (95% CI)
Received influenza vaccine alone		
IIV (n= 156)	3.8%	Ref
LAIV (n= 117)	2.6%	0.60 (0.15, 2.37)
No antipyretic use 8 hours before temperature taken		
IIV (n= 244)	4.1%	Ref
LAIV (n= 173)	2.9%	0.64 (0.22, 1.87)
Data only reported via text message used		
IIV (n= 214)	6.1%	Ref
LAIV (n= 149)	4.0%	0.57 (0.22, 1.45)
Age ≥ 3 year olds		
IIV (n=151)	6.6%	Ref
LAIV (n= 142)	4.2%	0.61 (0.23, 1.63)

Medical Record Review - Acute Care Visits

All participants (n=535) d0 through d10

- No febrile seizures or hospitalizations documented
- **9 ER Visits:**
  - **LAIV4 (n=2):** Viral Illness, Laceration
  - **IIV3 (n=3):** Pneumonia, Acute Vomiting, Acute Gastroenteritis
  - **IIV4 (n=4):** Blepharitis, Locking Thumb, Candida Diaper Dermatitis, Strep Throat/Asthma
- **17 Ambulatory Care Visits: LAIV4 (n=6), IIV3 (n=5), IIV4 (n=6)**

For participants with fever in d0 through d2 (n=22)

- **IIV4 (n=1):** Ambulatory Care d5: Allergic Reaction/URI
  ER d10: Strep Throat/Asthma
- **IIV3, Hep A (n=1):** ER d8: Acute Gastroenteritis

Fever LAIV/IIV Study: Summary

- No significant difference in fever rates T≥100.4˚F on vaccination day or in first 2 days post-vaccination with LAIV4 (3.8%) vs. IIV (5.8%) (IIV3 or IIV4)
  - Few fevers T ≥102.2˚F in study (4 IIV and 0 LAIV4)
- No significant difference in fever rates in the 3-10 days post-vaccination after LAIV vs. IIV
- No hospitalizations or febrile seizures in 0-10 days post-vaccination with any influenza vaccine
- Data analyses are ongoing