Safety of Live Attenuated Influenza Vaccine in Children with Asthma

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Advisory Committee on Immunization Practices (ACIP) Meeting
February 28, 2024

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- This study was supported by the CDC Clinical Immunization Safety Assessment (CISA) Project

- Dr. Creech reports the receipt of consulting fees from Pfizer, Moderna, Sanofi, GSK, TD Cowen Investments, and CommenseBio; grant support from Moderna; and royalties from UpToDate. None are related specifically to influenza vaccines or asthma

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abstract

BACKGROUND AND OBJECTIVES: Asthma is considered a precaution for use of quadrivalent live attenuated influenza vaccine (LAIV4) in persons aged ≥5 years because of concerns for wheezing events. We evaluated the safety of LAIV4 in children with asthma, comparing the proportion of children with asthma exacerbations after LAIV4 or quadrivalent inactivated influenza vaccine (IIV4).

METHODS: We enrolled 151 children with asthma, aged 5 to 17 years, during 2 influenza seasons. Participants were randomly assigned 1:1 to receive IIV4 or LAIV4 and monitored for asthma symptoms, exacerbations, changes in peak expiratory flow rate (PEFR), and changes in the asthma control test for 42 days after vaccination.

RESULTS: We included 142 participants in the per-protocol analysis. Within 42 days postvaccination, 18 of 142 (13%) experienced an asthma exacerbation: 8 of 74 (11%) in the LAIV4 group versus 10 of 68 (15%) in the IIV4 group (LAIV4-IIV4 = −0.0390 [90% confidence interval −0.1453 to 0.0674]), meeting the bounds for noninferiority. When adjusted for asthma severity, LAIV4 remained noninferior to IIV4. There were no significant differences in the frequency of asthma symptoms, change in PEFR, or childhood asthma control test/asthma control test scores in the 14 days postvaccination between LAIV4 and IIV4 recipients. Vaccine reactogenicity was similar between groups, although sore throat ($P = .051$) and myalgia ($P < .001$) were more common in the IIV4 group.

CONCLUSIONS: LAIV4 was not associated with increased frequency of asthma exacerbations, an increase in asthma-related symptoms, or a decrease in PEFR compared with IIV4 among children aged 5 to 17 years with asthma.

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Drs Sokolow and Stallings shared equal contribution as first author, conceptualized, designed, and oversaw the study, critically reviewed the analysis, drafted the initial manuscript, and revised the manuscript; Drs Harrington, Schlaudecker, Walter, Staat, Broder, and Creech conceptualized, designed, and oversaw the study, critically reviewed the analysis, drafted the initial manuscript, and revised the manuscript; Drs Kercsmar, Jimenez-Truque, and Moody helped design the initial study, helped conduct the study, reviewed study results, and provided revisions to the manuscripts; Dr Zhu designed the data collection instruments, drafted the statistical analysis plan, analyzed the data, and revised the manuscript; Ms Sokolow designed the data collection instruments, collected data, provided data query resolutions, and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This trial has been registered at www.clinicaltrials.gov (identifier NCT03600428).

DOI: https://doi.org/10.1542/peds.2021-055432

WHAT'S KNOWN ON THIS SUBJECT: Current recommendations caution against the use of live attenuated influenza vaccine (LAIV4) in children ≥5 years of age with asthma. Although LAIV4 has been associated with wheezing in young children, it is unclear whether LAIV4 increases the frequency of asthma exacerbations.

WHAT THIS STUDY ADDS: In this randomized, controlled trial in 5- to 17-year-old children with persistent asthma, live attenuated influenza vaccine was no more likely to be associated with asthma exacerbations than inactivated influenza vaccine.

To cite: Sokolow AG, Stallings AP, Kercsmar C, et al. Safety of Live Attenuated Influenza Vaccine in Children With Asthma. *Pediatrics.* 2022;149(4):e2021055432

Bottom Line, Up Front

In a study of 142 children with persistent asthma, **LAIV4 was not associated** with increased frequency of asthma exacerbations, increase in asthma-related symptoms, or decrease in peak expiratory flow rate (PEFR) in the 6 weeks following vaccination

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Asthma exacerbations among asthmatic children receiving live attenuated versus inactivated influenza vaccines

Vaccines 2017

G. Thomas Ray [a,*], Ned Lewis [a], Kristin Goddard [a], Pat Ross [a], Jonathan Duffy [b], Frank DeStefano [b], Roger Baxter [a], Nicola P. Klein [a]

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Live attenuated influenza vaccine use and safety in children and adults with asthma

Ann Allergy Asthma Immunol 2017

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3

Asthma and lower airway disease

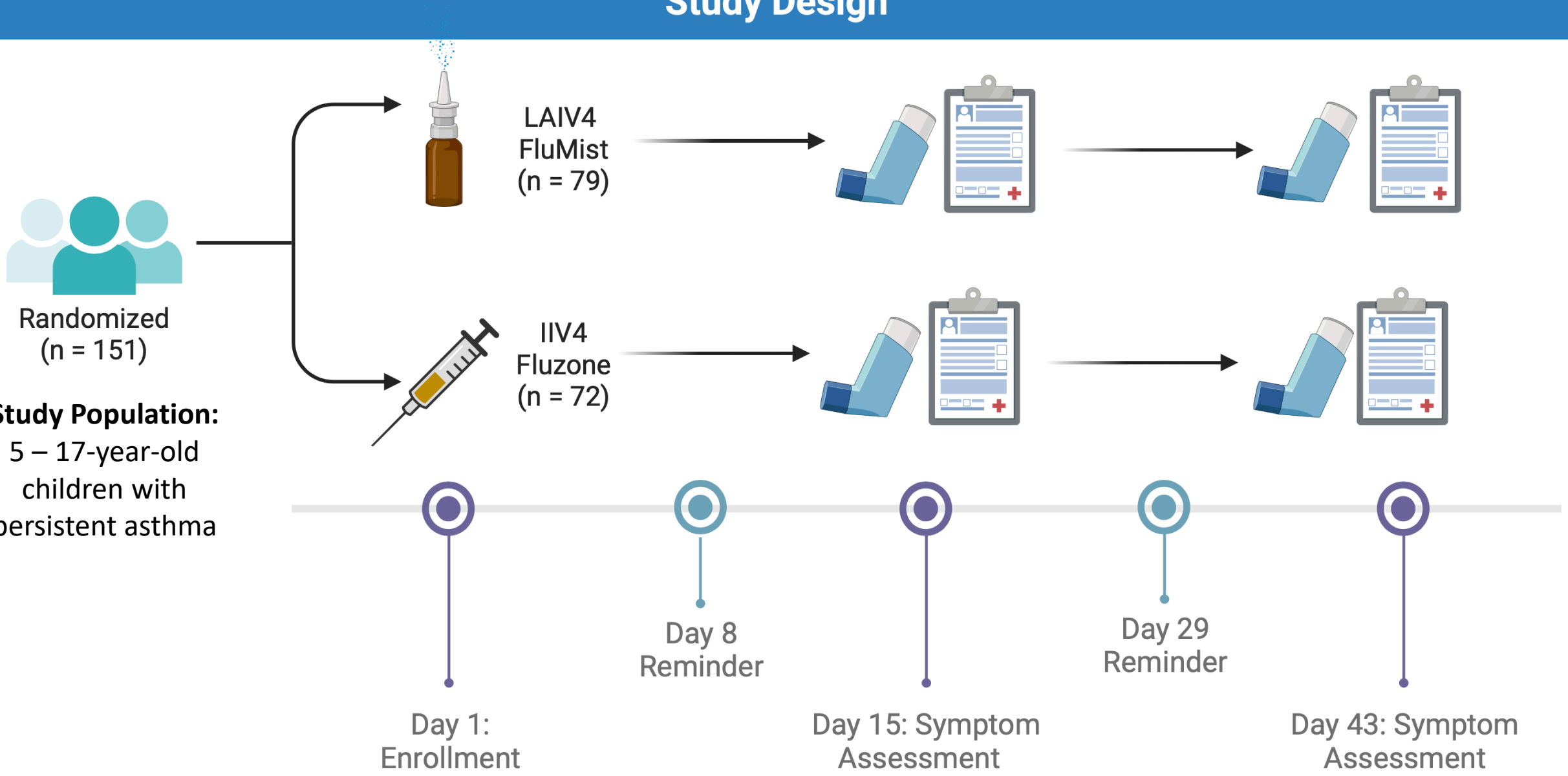
Safety of live attenuated influenza vaccine (LAIV) in children with moderate to severe asthma

JACI 2020

Paul J. Turner, FRACP, PhD,[a,b] Louise Fleming, MD,[a] Sejal Saglani, MD,[a] Jo Southern, PhD,[b] Nick J. Andrews, PhD,[b] and Elizabeth Miller, FRCPath,[b] on behalf of the SNIFFLE-4 Study Investigators *London, United Kingdom*

In these studies, children with asthma who received LAIV were not found to have a higher incidence of lower respiratory events

Study Design



Study Population:
5 – 17-year-old children with persistent asthma

Primary Objective and Definitions

To compare the proportion of participants experiencing an asthma exacerbation during the 42 days after LAIV4 vs. IIV4

- Scientific Hypothesis: LAIV4 is non-inferior to IIV4
- Null Hypothesis: Expressed statistically, the hypothesis was that the proportion of children experiencing an asthma exacerbation in the LAIV4 group would be ≥10% higher than the proportion in the IIV4 group.

Persistent Asthma: Provider diagnosis of asthma + prescription of a long-acting controller medication

- Note: This is distinct from *intermittent asthma*, in which children may have intermittent, mild symptoms or require infrequent doses of albuterol

Asthma Exacerbation: An acute episode of progressively worsening shortness of breath, cough, wheezing, chest tightness, or respiratory distress for which the patient seeks medical attention or receives a new prescription for systemic corticosteroids.

Relevant Exclusion Criteria

- Acute illness (with or without fever) within 72 hours of enrollment or use of antipyretics within 24 hours led to a temporary delay in vaccination
- Recent receipt of inactivated vaccine (14 days) or live vaccine (28 days) or planned receipt of any vaccine within 42 days of vaccination
- Children with immunosuppression, including those who had received 20 mg of prednisone (or greater) for more than 14 days in the previous month, were excluded.
- Children who had a life-threatening exacerbation in the previous 2 years or any exacerbation in the month prior to enrollment
- Use of influenza-specific antiviral medication within 48 hours of enrollment
- Currently receiving aspirin

Additional Eligibility Issues

Post-menarchal females had urine or serum pregnancy testing prior to enrollment

For children 5-8 years of age who required two doses of vaccine based upon ACIP recommendations, enrollment could occur after either the first or the second dose of vaccine.

- If enrollment occurred after the first dose, the study staff instructed the family to delay 2nd vaccination until after study follow-up was completed unless widespread influenza disease activity was detected in the community.

TABLE 1 Baseline Characteristics by Study Arm

	LAIV4, $N = 79$	IIV4, $N = 72$	Combined, $N = 151$	P
Asthma severity status				.38[a]
Mild	26 (33)	19 (26)	45 (30)	
Moderate or severe	53 (67)	53 (74)	106 (70)	
Baseline ACT/cACT score	21.76 (±3.17)	20.99 (±4.05)	21.39 (±3.62)	.4[b]
Age group, y				.67[a]
5–11	58 (73)	55 (76)	113 (75)	
12–17	21 (27)	17 (24)	38 (25)	
Age, y, median (IQR)	9 (7–12)	9 (7–11)	9 (7–12)	.59[b]
Sex				.50[a]
Male	44 (56)	44 (61)	88 (58)	
Female	35 (44)	28 (39)	63 (42)	
Ethnicity				.79[a]
Hispanic or Latino	4 (5)	3 (4)	7 (5)	
Not Hispanic or Latino	75 (95)	69 (96)	144 (95)	
Race				.51[a]
Asian	2 (3)	0	2 (1)	
Black	25 (32)	24 (33)	49 (32)	
White	43 (54)	42 (58)	85 (56)	
Multiple races	9 (11)	6 (8)	15 (10)	
BMI, years, median (IQR)	19.5 (16.5–22.9)	18.6 (16.2–21.6)	18.7 (16.3–22.5)	.56[b]

Values expressed as *n* (%) unless otherwise indicated. IQR, interquartile range

[a] Pearson χ-square test

[b] Wilcoxon rank test

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[b] Wilcoxon rank test

70% of participants were classified as having moderate or severe asthma

There were slightly more males than females (p=0.5)

Black individuals comprised >30% of the study population; approximately 5% were Hispanic or Latino

In the **14 days** following vaccination, we observed 3 exacerbations among LAIV4 recipients and 4 in IIV4 recipients (3.9% vs. 5.7%, p=0.74)

In the **42 days** following vaccination, we observed 8 exacerbations in the LAIV4 group and 10 in the IIV4 group (10.8% vs. 14.7%, p=0.71)

TABLE 2 Asthma Exacerbations in the 14 and 42 Days Postvaccination With LAIV4 or IIV4 by Study Arm and Baseline Severity

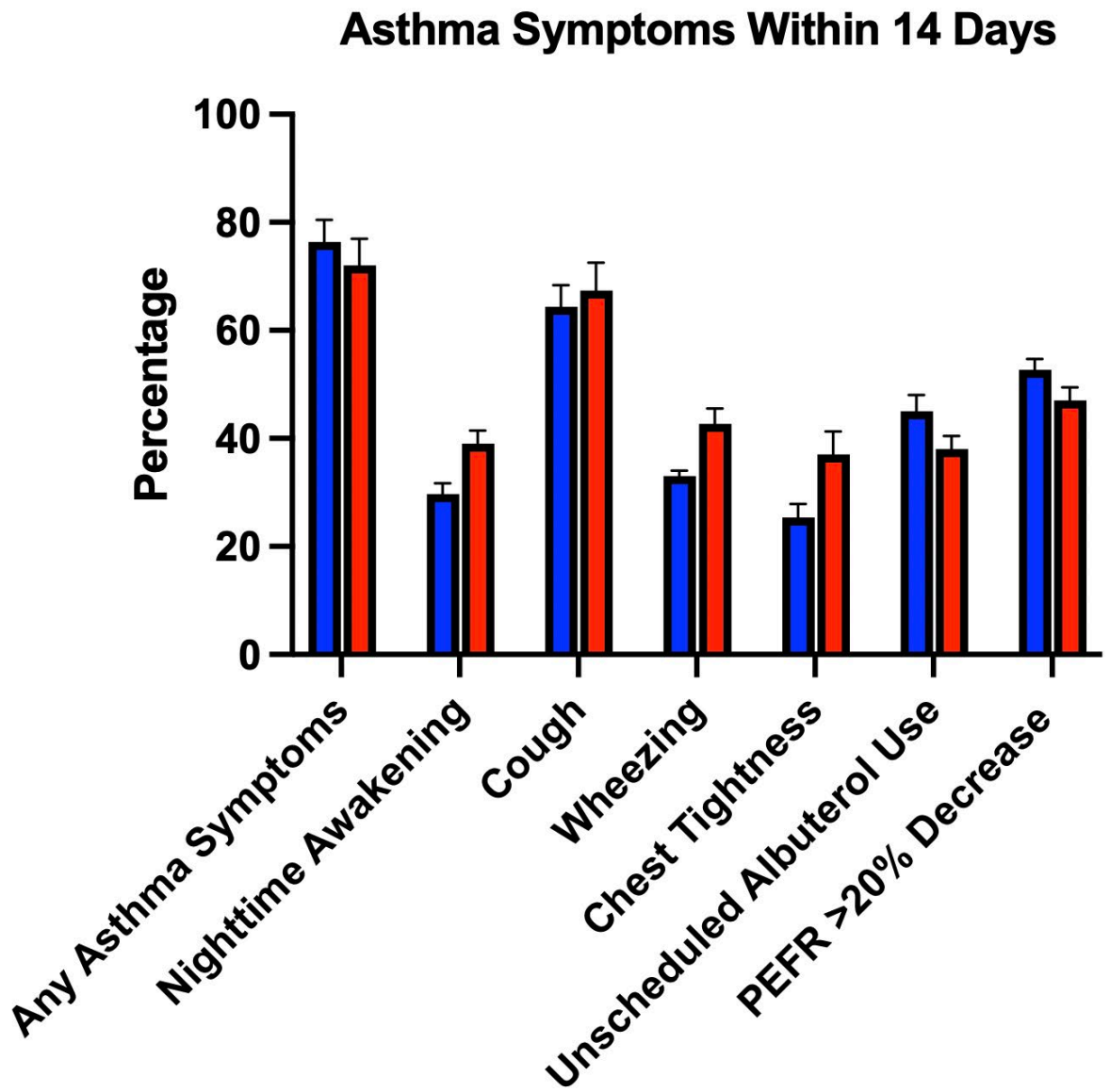
Asthma Severity at Baseline		14 d Exacerbation[a]		*P*		43 d Exacerbation[a]		*P*
Mild	*N* = 44	LAIV4 (*n* = 26)	IIV4 (*n* = 18)	—	*N* = 41	LAIV4 (*n* = 25)	IIV4 (*n* = 16)	—
		0	0			1 (1.3%)	3 (4.4%)	
Moderate or severe	*N* = 102	LAIV4 (*n* = 50)	IIV4 (*n* = 52)	—	*N* = 101	LAIV4 (*n* = 49)	IIV4 (*n* = 52)	—
		3 (3.9%)	4 (5.7%)			7 (9.5%)	7 (10.3%)	
All participants	*N* = 146	3 (3.9%)	4 (5.7%)	.74	*N* = 142	8 (10.8%)	10 (14.7%)	.71

—, not applicable.

[a]Asthma exacerbation was defined as any acute episode of progressively worsening shortness of breath, cough, wheezing, chest tightness, and/or respiratory distress after influenza vaccination for which the participant sought unscheduled medical attention or received a new prescription for systemic corticosteroids.

Given that the upper bound for non-inferiority was 10% (0.1), a difference in proportion of -3.9% (CI: 90% CI: -0.15, 0.07) means that we can ***reject the null hypothesis*** *that LAIV4 is inferior to IIV4.*

LAIV4 was not associated with increased asthma symptoms



No significant differences were seen when comparing across age groups (5-11 years of age, 12-17 years of age), study site, or asthma severity (mild/moderate vs. severe)

PEFR: Peak Expiratory Flow Rate

Myalgia and sore throat were more common in IIV4 recipients

SUPPLEMENTAL TABLE 3 Frequency of Solicited Adverse Events by Vaccine Group

	LAIV4 $N = 76$	IIV4 $N = 70$	Total $N = 146$	*P*
Rhinorrhea				.68
None	30.3 (23)	40.0 (28)	34.9 (51)	
Mild	46.1 (35)	32.9 (23)	39.7 (58)	
Moderate	21.1 (16)	18.6 (13)	19.9 (29)	
Severe	2.6 (2)	8.6 (6)	5.5 (8)	
Sore throat				.051
None	71.1 (54)	58.6 (41)	65.1 (95)	
Mild	25.0 (19)	25.7 (18)	25.3 (37)	
Moderate	3.9 (3)	8.6 (6)	6.2 (9)	
Severe	0.0 (0)	7.1 (5)	3.4 (5)	
Headache				.41
None	57.9 (44)	50.0 (35)	54.1 (79)	
Mild	28.9 (22)	35.7 (25)	32.2 (47)	
Moderate	9.2 (7)	11.4 (8)	10.3 (15)	
Severe	3.9 (3)	2.9 (2)	3.4 (5)	
Myalgia				<.001
None	88.2 (67)	64.3 (45)	76.7 (112)	
Mild	6.6 (5)	22.9 (16)	14.4 (21)	
Moderate	5.3 (4)	10.0 (7)	7.5 (11)	
Severe	0.0 (0)	2.9 (2)	1.4 (2)	
Fever				.11
None	97.4 (74)	91.4 (64)	94.5 (138)	
100.4–100.9°F	1.3 (1)	1.4 (1)	1.4 (2)	
101–102.1°F	1.3 (1)	7.1 (5)	4.1 (6)	

Strengths and Limitations of the Study

Strengths

- Multicenter, prospective, randomized, and controlled
- Enriched for children with persistent asthma and those with moderate to severe asthma
- Captured asthma symptoms in addition to asthma exacerbations and medical utilization
- Captured reactogenicity data
- Enrolled over two influenza seasons, increasing generalizability

Limitations

- Enrolled fewer participants than originally intended, but posterior power calculations revealed adequate power (79%) to detect differences between groups
- Enrolled over two influenza seasons, leading to slightly different products

Summary and Conclusions

1. LAIV4 was not associated with increased asthma symptoms or asthma exacerbations in the 14- or 42-days following immunization

2. Rates of reactogenicity were similar between IIV4 and LAIV4, though myalgia and sore throat were more common in the IIV4 arm

3. LAIV4 may be a suitable option for children ≥5 years with asthma, including moderate to severe asthma

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Discussion