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Safety of Live Attenuated Influenza Vaccine in Children With 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).

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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).

CONFLICT OF INTEREST DISCLOSURES: The authors report no financial conflicts of interest relevant to this work.

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.

Asthma is a leading cause of childhood hospitalization and utilization of medical resources in the United States and is one of the most common chronic diseases of childhood. Viral infections are among the most common triggers of asthma exacerbations in children, including rhinovirus, respiratory syncytial virus, and influenza viruses.[1–3] The risk of influenza infection can be reduced through vaccination, and the Centers for Diseases Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for all persons ≧6 months of age, including children with asthma, for whom there are no other contraindications.[4]

Inactivated influenza vaccines (IIV) are the most commonly administered influenza vaccines in children[5]; however, quadrivalent live-attenuated influenza vaccine (LAIV4) offers an alternative for children ≥2 years of age. Although a provider diagnosis of asthma or a wheezing episode in the past year is an ACIP-recommended contraindication to receipt of LAIV4 between 2 and 4 years of age,[4] it remains unclear whether LAIV may be appropriate for children 5 years of age and older with asthma, for whom there is currently a precaution to receiving LAIV. Early studies of LAIV suggested a higher incidence of wheezing in LAIV recipients compared with IIV recipients.[6] These early reports of LAIV-associated wheezing occurred primarily in young children, and formal assessments of wheezing in children with asthma have only recently been performed. A recent prospective study completed in the United Kingdom evaluated the safety of LAIV in children with moderate to severe asthma and found no significant change in asthma control 4 weeks after LAIV4 administration.[7] This study was limited in that it did not compare similar patients receiving IIV4. Similarly, Nordin et al compared LAIV4 with IIV4 in children with asthma and found no increase in the incidence of lower respiratory events during the 42 days postvaccination, although this study was limited by its retrospective nature.[8]

The primary objective of this prospective clinical trial was to compare the proportion of participants with asthma exacerbations postimmunization among children with persistent asthma, 5 to 17 years of age, who received LAIV4 versus IIV4.

METHODS

Participants were enrolled from October 15, 2018 to December 31, 2019 at 3 trial sites (Vanderbilt University Medical Center, Nashville, TN, Duke University Health System, Durham, NC, and Cincinnati Children's Hospital Medical Center, Cincinnati, OH). Children 5 to 17 years of age with a current diagnosis of persistent asthma were considered eligible for the study. Persistent asthma was defined as provider-diagnosed asthma and the current use of daily controller medication. Participants were in good health, other than asthma, as determined by medical history. Postmenarchal female participants were required to have a negative pregnancy test within 24 hours before vaccination.

After informed consent and assent were obtained, participants were randomly assigned 1:1 to receive either a single intranasal dose of LAIV4 (FluMist® Quadrivalent, AstraZeneca) or an intramuscular injection of IIV4 (Fluzone® Quadrivalent Vaccine, Sanofi Pasteur). Randomization was stratified by age group (5 to 11 vs 12 to 17 years of age) and asthma severity (mild versus moderate/severe). Children receiving either low-dose inhaled corticosteroids (ICS) or montelukast were considered to have mild, persistent asthma. Children receiving low-dose ICS plus montelukast, low-dose ICS plus a long-acting β-agonist, or medium-dose ICS were defined as moderate persistent asthma. Children receiving medium-dose ICS plus montelukast or long-acting β-agonist, any high-dose ICS, omalizumab or mepolizumab, or chronic system steroids were defined as having severe asthma. This categorization was adapted from the 2011 National Asthma Education and Prevention Program expert panel. Categorization of low-, medium-, and high-dose steroid ICS was based on doses listed in the report.[9] In the 2018 to 2019 season, only children 5 to 11 years of age were enrolled; in the second season (2019–2020), the study was expanded to include children 5 to 17 years of age. The permuted block randomization scheme was prepared separately for each clinical trial site, with a varying block size of either 4 or 6. Randomization was performed by using REDCap,[10] hosted at Vanderbilt University Medical Center. The study was open-label and neither study staff nor participants were blinded to treatment arm assignments.

The primary outcome of asthma exacerbation was defined as any acute episode of progressively worsening shortness of breath, cough, wheezing, chest tightness, and/or respiratory distress during the 42 days after influenza vaccination, for which the participant sought unscheduled medical attention (eg, health care provider office, emergency department visit, or hospitalization) or received a new prescription for systemic corticosteroids. Outcomes of unscheduled albuterol use, the number of participants who experienced a clinically significant decrease in peak expiratory flow rate (PEFR), changes in the asthma control test (ACT) for children 12 to 17 years of age or childhood asthma control test (cACT) for children 5 to 11 years of age, and the rates of medical utilization for asthma-related symptoms during the 42 days after vaccination between the 2 groups were captured via participant report. Local and systemic reactogenicity events, asthma symptoms,

unscheduled albuterol use, PEFR measurements, and medical utilization were captured daily through 14 days after vaccination.

Two populations were defined. The intention-to-treat population included 151 participants who were enrolled, randomly assigned, and received a study vaccine at visit 1. The per-protocol population at 15 days and 43 days are subsets of the intention-to-treat population. These populations were defined as all participants who were randomly assigned, vaccinated, had completed the study procedures through day 15 or 43, had no protocol deviations that were likely to affect the study objectives, and who did not receive a second dose of influenza vaccine before day 43.

The study was designed to enroll 270 participants based on assumptions that 12% of children would experience asthma exacerbations after vaccination[11] and that 10% would be lost to follow-up. The null hypothesis for the study was that the proportion of children experiencing asthma exacerbation in the LAIV4 group would be ≥10% higher than the proportion in the IIV4 group. The study was designed to provide >80% power to claim noninferiority with a 1-sided α of 0.05. Given the smaller sample size enrolled in the study, posterior power calculations were also performed, revealing 78.6% power to detect a difference in the proportion of children experiencing asthma exacerbations between groups. Descriptive analyses were used to summarize continuous variables with mean, standard deviation, median, and interquartile ranges. Categorical variables were summarized with frequencies and percentages. Comparisons of demographic characteristics between LAIV4 and IIV4 groups were conducted by using Pearson χ^2 and Wilcoxon rank tests, as appropriate.

The human subject protection programs at Vanderbilt University Medical Center, Cincinnati Children's Hospital Medical Center, and Duke University Health System, and the CDC approved the study before any study-related activities occurred. The trial was registered at ClinicalTrials.gov (NCT03600428).

RESULTS

One hundred fifty-one participants were enrolled over 2 influenza seasons (Fig 1): 52 children from 2018 to 2019 and 99 children from 2019 to 2020. Late release and reduced availability of LAIV4, particularly in 2018 to 2019, and lack of parental willingness to participate were the most common reasons for low enrollment. Baseline characteristics of participants are provided in Table 1.

Within 42 days postvaccination, 18 of 142 (12.7%) of participants experienced an asthma exacerbation: 8 of 74 in the LAIV4 group (10.8%) versus 10 of 68 in the IIV4 group (14.7%) (Table 2). The risk difference of LAIV4 and IIV4 was −0.0390 (90% confidence interval: −0.1453 to 0.0674). As the upper bound of the confidence interval was <0.1 (10%), we reject the null hypothesis that LAIV4 is inferior to IIV4 regarding the proportion of participants experiencing asthma exacerbation in the 42 days postvaccination. When adjusted for asthma severity (mild versus moderate or severe), LAIV4 remained noninferior to IIV4. Among children with mild asthma, 1 of 25 (4.0%) in the LAIV4 group versus

3 of 16 (19.8%) in the IIV4 group experienced an exacerbation within 42 days; among those with moderate or severe asthma, 7 of 49 (14.3%) in the LAIV4 group experienced an exacerbation versus 7 of 52 (13.5%) in the IIV4 group. Table 2 also reveals the frequency of asthma exacerbation within 14 days of vaccination. Similarly, LAIV4 was found to be noninferior to IIV4.

Next, we evaluated the proportion of subjects with any asthma-related symptoms within 14 days of vaccine administration (Fig 2). There were no significant differences in the frequency of nighttime awakening, unscheduled albuterol use, cough, wheezing, or chest tightness in the 14 days postvaccination between the 2 vaccine groups. There were slightly more wheezing episodes among IIV4 recipients than LAIV4 recipients, but this was not statistically significant.

To evaluate asymptomatic changes in pulmonary function, we measured peak expiratory flow rate (PEFR) daily after vaccination. The proportions of individuals experiencing a ≥20% decrease in PEFR in the 14 days after vaccination were not statistically different between LAIV4 and IIV4 groups (Fig 2). Similarly, changes in cACT or ACT scores from baseline through 42 days were not statistically different between LAIV4 and IIV4 groups or between asthma severity levels.

Rates of medical utilization for asthma-related symptoms during the 14 ($P = .737$) and 42 days ($P = .735$) after vaccination did not significantly differ between LAIV4 and IIV4 groups after adjusting for asthma severity levels. Proportions of vaccine systemic reactogenicity events during the 14 days after vaccination were not different between LAIV4 and IIV4 groups (Supplemental Table 3), except myalgia ($P < .001$) and sore throat ($P = .051$), which were more common in the IIV4 group.

DISCUSSION

In this prospective, open-label clinical trial comparing LAIV4 and IIV4 in children with persistent asthma, LAIV4 was noninferior to IIV4 in regard to asthma exacerbations in the 42 days after vaccination. In addition, the frequency of asthma-related symptoms, changes in PEFR, and change in asthma symptom scores were low, overall, and were similar between the 2 groups. These data add to the compelling safety record of LAIV in children, including those with persistent asthma.

Initial concerns over the safety of LAIV among children with asthma stemmed from the results of a larger randomized, double-blind, placebo-controlled safety trial in healthy children conducted by Bergen et al.[6] Children were randomly selected 2:1 to receive either LAIV or placebo; enrolled children were followed for 42 days after each vaccination for all medically attended events. A total of 9689 children were enrolled in the study. Among the participants, no acute respiratory tract events were associated with receipt of vaccine; however, LAIV receipt was associated with a 4-fold increase in the risk of reactive airway disease in children 18 to 35 months of age (relative risk 4.06; 90% confidence interval, 1.29 to 17.86). Although the Bergen study was not designed to evaluate safety in children with asthma explicitly, nor compare LAIV with IIV, it raised concern about the safety of

administering LAIV to this population. Because of this safety concern, subsequent studies have attempted to evaluate whether LAIV can safely be administered to this group.

One of the largest of these studies was an open-label study conducted among 2229 asthmatic children aged 6 to 17 years by Fleming et al during the 2002 to 2003 influenza season.[11] No significant differences were reported between the LAIV and IIV vaccine recipients in the incidence of asthma exacerbation during 42 days after vaccination, mean peak expiratory flow rates, asthma symptom scores, or nighttime awakening scores. Overall, there was no evidence of an increase in adverse pulmonary outcomes for LAIV compared with IIV, and LAIV had a significantly greater relative efficacy of 35% compared with IIV in this high-risk population.

Ray et al used a retrospective analysis in a single large health organization to review the influenza vaccine history of >150 000 children with a past or present history of asthma, aged 2 to 15 years.[12] With a dataset of >387 000 immunizations, they found no evidence of increased exacerbations after LAIV over IIV. This finding remained the same for each asthma group classification: current/persistent, current/not persistent, and remote history (only) of asthma. Similarly, by using the Vaccine Safety Datalink to query the records of >6 million individuals (5.9% with asthma), Duffy et al evaluated the incidence rate ratio of medically attended respiratory events in the 14 days after receipt of LAIV.[13] Safety data were available from >12 000 doses of LAIV, 93% in those with intermittent or mild asthma. In this study, LAIV use was not associated with an increased risk of medically attended respiratory events.

In a prospective manner, Turner et al evaluated 478 pediatric patients with physician-diagnosed asthma who were administered LAIV.[7] Asthma control and frequency of asthma exacerbations in the 4 weeks after immunization served as outcome measures of interest. Fifteen percent of participants reported an asthma exacerbation in the 4 weeks after LAIV administration; neither asthma severity nor asthma control at the time of vaccination predicted exacerbation occurrence, and no statistically significant changes were noted in the ACT/cACT between the time of immunization and 4 weeks postimmunization. Additionally, in an open-label study of nearly 800 children with egg allergy (including 445 with physician-diagnosed asthma), LAIV was associated with lower respiratory tract symptoms within 72 hours of vaccination in 62 participants (8.1%), including 29 with parent-reported wheezing events.[14] Importantly, neither of these studies included a control arm (whether placebo or IIV); therefore, it is difficult to determine the extent to which LAIV was truly causal to these events.

Building off these previous studies, our prospective study suggests that LAIV may be appropriate for some children with asthma. Our study revealed overall low rates of asthma exacerbations in the 42 days after influenza vaccination, regardless of formulation, in >150 participants spanning 2 distinct influenza seasons and preferentially enrolling children with moderate to severe asthma. In addition, symptoms such as cough, nighttime awakenings, unscheduled albuterol use, wheezing, chest tightness, change in cACT/ACT scores, or significant decreases in PEFR 14 days after vaccination were also comparable between groups. There was no observed difference for medical utilization postvaccine for asthma-

related symptoms in either group, and the overall incidence of medical utilization based on severity group was low (0% in mild asthma; 4% in moderate/severe) and not clinically or statistically different between vaccine arms.

We recognize there are certain limitations to this study. Change in ACIP policy and late release of LAIV in the first year delayed study initiation because of concerns over LAIV4 efficacy. Reduced provider and parental confidence in LAIV4 remained after a subsequent new recommendation was made and LAIV4 was reintroduced. Therefore, we conducted the study over 2 seasons to improve enrollment, leading to evaluation of slightly different vaccine products, although this can also be considered a strength of the study given that we were able to evaluate the quadrivalent formulation rather than the previously studied trivalent formulation. Although we enrolled fewer participants than originally intended, posterior power calculations reveal adequate power (79%) to detect differences between groups. Despite these limitations and reduced sample size, we were able to establish noninferiority of LAIV4 compared with IIV4 in postimmunization asthma exacerbations.

CONCLUSIONS

In pediatric patients ≥5 years of age with persistent asthma, including moderate-to-severe asthma, LAIV4 was not associated with increased frequency of asthma exacerbations, increase in asthma-related symptoms, or decrease in PEFR compared with IIV4. These data support reexamining precautions to using LAIV4 in children with asthma, which could be particularly important during influenza pandemics, at times when IIV4 supplies are limited, in situations of public/school mass vaccination clinics using LAIV, or for children with significant needle aversions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
ACT	asthma control test
cACT	childhood asthma control test
CDC	Centers for Disease Control and Prevention
ICS	inhaled corticosteroids
IIV4	inactivated influenza vaccine
LAIV4	live attenuated influenza vaccine
PEFR	peak expiratory flow rate

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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.

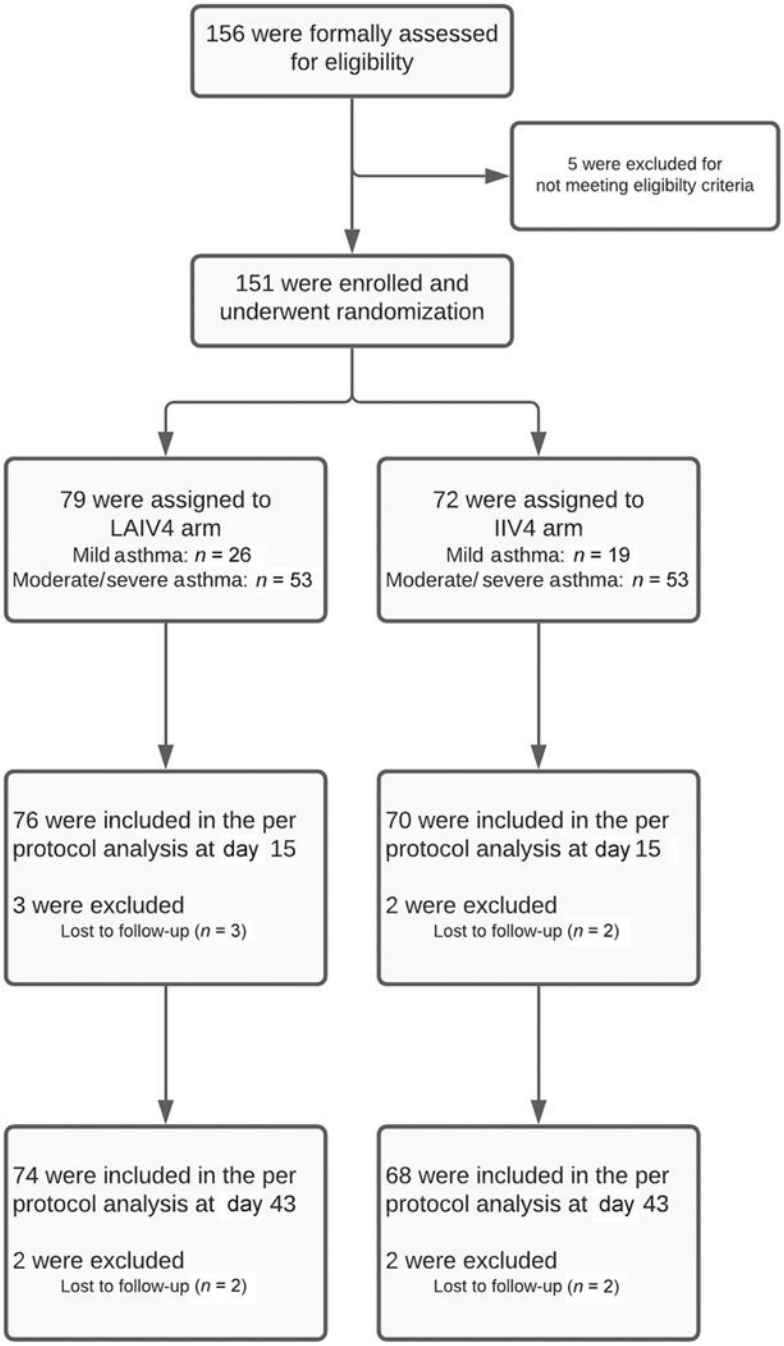

FIGURE 1.
CONSORT diagram.

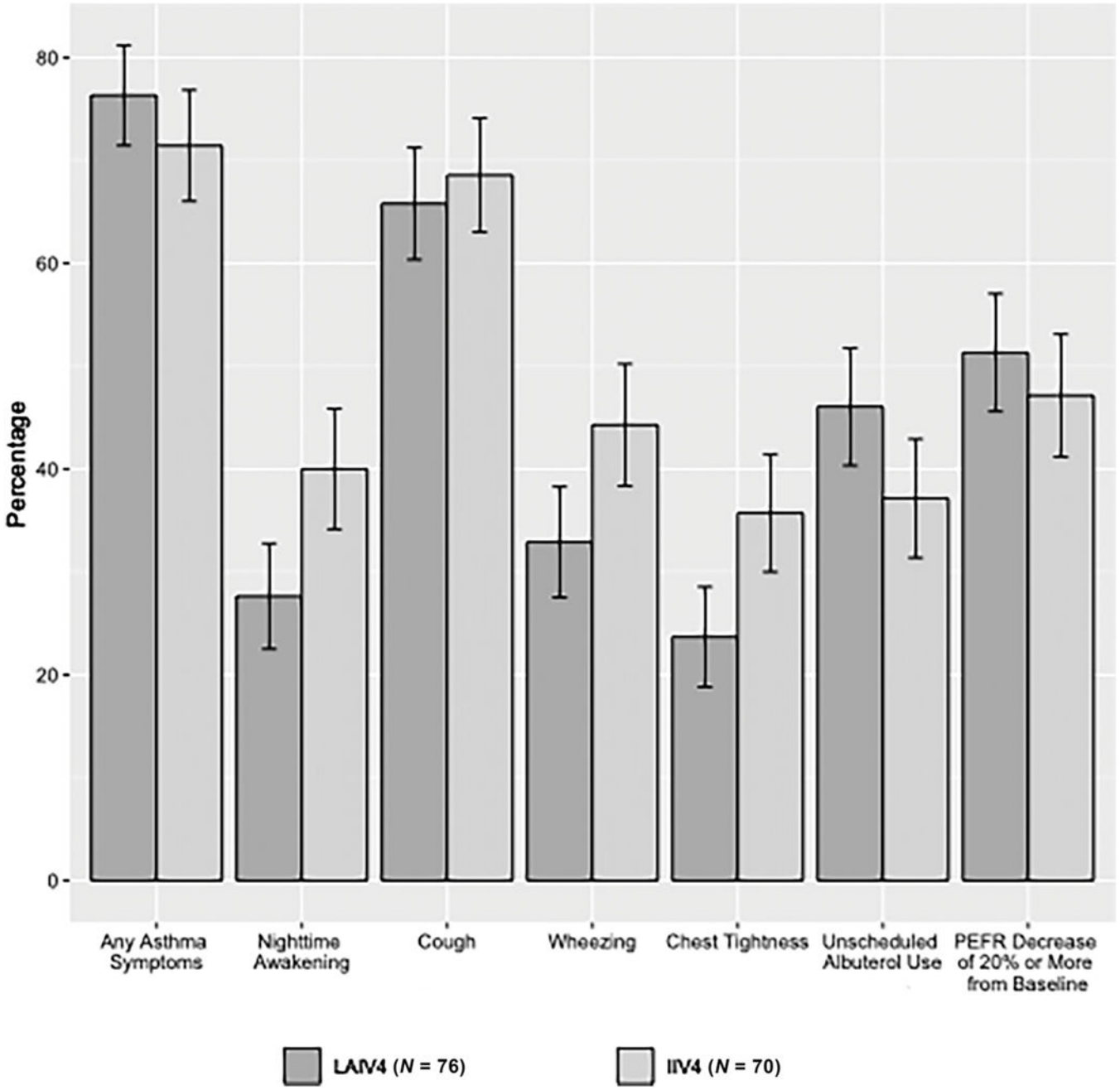

FIGURE 2.

Asthma-related symptoms, by participant and parental report, in the 14 days after immunization, with corresponding error bars.

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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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.

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