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Safety of Russian-backbone seasonal trivalent, live-attenuated influenza vaccine in a phase II randomized placebo-controlled clinical trial among children in urban Bangladesh

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ABSTRACT

Introduction: Live-attenuated influenza vaccines (LAIVs) have the potential to be affordable, effective, and logistically feasible for immunization of children in low-resource settings.
Material and methods: We conducted a phase II, randomized, double-blind, parallel group, placebo-controlled trial on the safety of the Russian-backbone, seasonal trivalent LAIV among children aged 24 through 59 months in Dhaka, Bangladesh in 2012. After vaccination, we monitored participants for six months with weekly home visits and study clinic surveillance for solicited and unsolicited adverse events, protocol-defined wheezing illness (PDWI), and serious adverse events (SAEs), including all cause hospitalizations.
Results: Three hundred children were randomized and administered LAIV ($n = 150$) or placebo ($n = 150$). No immediate post-vaccination reactions occurred in either group. Solicited reactions were similar between vaccine and placebo groups during the first 7 days post-vaccination and throughout the entire trial. There were no statistically significant differences in participants experiencing PDWI between LAIV and placebo groups throughout the trial ($n = 13$ vs. $n = 16$, $p = 0.697$). Of 131 children with a history of medical treatment or hospitalization for asthma or wheezing at study entry, 65 received LAIV and 66 received placebo. Among this subset, there was no statistical difference in PDWI occurring throughout the trial between the LAIV or placebo groups (7.7% vs. 19.7%, $p = 0.074$). While there were no related SAEs, LAIV recipients had six unrelated SAEs and placebo recipients had none. These SAEs included three due to traumatic injury and bone fracture, and one each due to accidental overdose of paracetamol, abdominal pain, and acute gastroenteritis. None of the participants with SAEs had laboratory-confirmed influenza, wheezing illness, or other signs of acute respiratory illness at the time of their events.
Conclusions: In this randomized, controlled trial among 300 children aged 24 through 59 months in urban Bangladesh, Russian-backbone LAIV was safe and well tolerated. Further evaluation of LAIV safety and efficacy in a larger cohort is warranted.

1. Introduction

About 1.8% of infant deaths globally are attributed to influenza virus infection [1], and 99% of early childhood deaths due to severe influenza virus infection occur in developing countries [2]. Nevertheless, most low- and middle-income countries have no policies regarding prevention of seasonal influenza virus infection [3].

Influenza vaccines are effective at preventing influenza disease, particularly in young children [4]. Superior efficacy of FluMist®, a live-attenuated influenza vaccine (LAIV) based on the influenza A/Ann Arbor/6/60 H2N2 and influenza B/Ann Arbor/1/66 backbones (Ann Arbor-backbone LAIV), as compared to inactivated influenza vaccine has been demonstrated in children in three randomized controlled efficacy trials [5–7]. However, because

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of excess wheezing and hospitalization events occurring in vaccinated children younger than two years of age, FluMist® is licensed for persons two years of age and older [8]. The same Ann Arbor-backbone LAIV is also sold as Fluenz in some countries

A second LAIV was developed in the former Soviet Union from attenuated influenza A/Russian/134/57 (H2N2) and influenza B/USSR/60/69 master donor viruses (Russian-backbone LAIV), has been approved for use in children since the 1980s [9]. Russian-backbone LAIV seed strains have been provided to developing country vaccine manufacturers through an intellectual property transfer program initiated by WHO [10]. The Serum Institute of India, Ltd. (SIIL[1]) has recently developed a seasonal trivalent LAIV, which is approved for use in India for persons 2 years of age and over [11]. The potential for excess wheezing illness following receipt of the Russia-backbone LAIV is not known. We conducted a clinical trial of the SIIL trivalent, seasonal, LAIV among children in Dhaka, Bangladesh to evaluate vaccine safety, with a particular emphasis on wheezing adverse events. Additional virus shedding and immunogenicity studies were performed which provided strong evidence of a relatively high take rate for all three vaccine strains [12]. They will be described in a separate publication. The trial was designed to inform a clinical efficacy trial planned for the same community if LAIV were demonstrated to be safe and well tolerated.

2. Materials and methods

2.1. Ethics

This study was reviewed and approved by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) Research Review and Ethics Review Committees (Dhaka, Bangladesh) and the Western Institutional Review Board (Olympia, WA, USA). The Good Clinical Practice guidelines of the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) were followed. The study objectives, methodology, possible inconveniences, and risks were explained to participant parents or guardians in the local language (Bangla). The study was registered with ClinicalTrials.gov (NCT01625689).

2.2. Study design

This was a phase II, randomized, double-blind, parallel group, placebo-controlled trial on the safety of the SIIL Russian-backbone LAIV among children in Dhaka, Bangladesh. The co-primary objectives were: (1) to compare the proportion of solicited and unsolicited reactions among children receiving LAIV and placebo within the first 7 days and 6 months of -vaccination, respectively; and (2) to compare the proportion of serious adverse events (SAEs) and protocol-defined wheezing illness (PDWI) among children receiving LAIV and placebo through 42 days and 6 months of vaccine administration.

2.3. Participants

Children living in Kamalapur Field Site in urban Dhaka were recruited for this study [13,14]. Inclusion criteria included: (1) healthy male or female child at least 24 months of age and no older than 59 months of age at the time of study vaccination; (2) residence in the study area; and (3) parent or guardian willing to provide written informed consent prior to the participant's study vaccination. Exclusion criteria included: (1) any serious chronic disease; (2) receiving immunosuppressive agents during the two weeks prior to study vaccination; (3) documented hypersensitivity to eggs or other components of the vaccine or life-threatening reactions to previous influenza vaccinations; (4) receiving aspirin therapy currently or two weeks before; (5) living in a household with somebody currently participating in a respiratory pathogen vaccination or antiviral study; (6) current or past participation (within 2 months of trial enrollment visit) in any clinical trial involving a drug or biologic with activity against respiratory disease; or (7) any condition determined by the investigator as likely to interfere with evaluation of the vaccine or to be a significant potential health risk to the child.

2.4. Randomization and blinding

This trial was randomized in a 1:1 ratio of LAIV to placebo. Both vaccines were identical in presentation and masked to conceal LAIV and placebo identification. Neither the study physician administering the vaccine, the participant and family, staff evaluating clinical illness, nor staff conducting medical monitoring had access to the vaccine allocation. The vaccinating physician had no involvement in subsequent vaccine safety or clinical evaluations.

2.5. Vaccine

SIIL donated the LAIV and placebo (lot numbers 166E2001 and E9001PCB). The active vaccine used the Russian master donor virus backbone and the placebo contained all components of the vaccine without the influenza viruses included. LAIV strains were cold-adapted to replicate at 25–33 °C, temperature sensitive to restrict replication ≥40 °C, and attenuated [15]. LAIV contained the hemagglutinin and neuraminidase of the WHO recommended vaccine strains for the 2011–2012 Northern Hemisphere influenza season [16]. Concentrations of vaccine components were not less than 10^7 EID_{50}/dose for influenza A components and not less than $10^{6.5}$ EID_{50}/dose for the influenza B component. At the time of vaccination, a study physician reconstituted the vaccine with sterile water diluent and administered in a 0.5 ml intranasal dose (one spray of 0.25 ml per nostril) via a single-use sprayer device. A single dose of vaccine was administered per manufacturer recommendations.

2.6. Safety evaluation and definitions

Participants were enrolled from June 21, 2012 through July 15, 2012. Those who consented and met eligibility criteria received a single dose of study vaccine and were then observed for 30 min for immediate adverse events. Field Research Assistants (FRAs) monitored solicited (nasal congestion/runny nose, stuffy nose, ear pain, cough, headache, fever, irritability, nausea, sore throat, lethargy) and unsolicited adverse events during daily home visits for the first 7 days post-vaccination. This duration of daily monitoring was chosen because in preceding phase II/III SIIL LAIV clinical trials, imbalances in the solicited adverse events had resolved by 7 days. FRAs subsequently assessed for solicited adverse events through weekly home visits through the remainder of the trial. Through December 2012, FRAs assessed unsolicited adverse events during weekly home visits, and study physicians did the same during clinical evaluations of children receiving care at the study health clinic. SAEs were monitored throughout the trial. Adverse events were graded for severity by FRAs with the exception of SAEs and PDWIs, which were graded by study physicians. Adverse events were graded as mild, moderate, severe, or life-threatening, using standardized grading scales, except for subjective fever, lethargy, and tachypnea occurring after the first week post-vaccination which were graded as present/absent only. During home visits, participants were recommended to seek further evaluation by study physicians when FRAs determined that participants met referral

[1] Nonstandard abbreviations used in text: FRA: Field Research Assistants PDWI: Protocol-Defined Wheezing Illness SIIL: Serum Institute of India, Ltd.

criteria which were defined as either of the following: (1) any of fever (≥38 °C axillary), tachypnea (≥40 breaths/min), chest indrawing, lethargy, cyanosis, inability to drink, convulsions, difficult breathing, noisy breathing, ear pain or discharge; or (2) presence of both cough and runny nose.

Study physicians examined all participants meeting referral criteria and presenting to the study clinic (whether referred by FRAs or self-referred) and used a standardized, data collection instrument to document history of present illness and clinical findings. PDWI was defined as illness among participants meeting referral criteria, evaluated by study physicians in the study clinic or participating hospital, and characterized by a long, high-pitched whistling or musical sound on expiration heard by auscultation over the lung fields. PDWI severity was determined by study physicians and defined as mild (wheezing illness without other findings associated with moderate or greater severity disease), moderate (nasal flaring, chest in-drawing, or pulse oximetry 90–95%), severe (dyspnea at rest causing inability to perform usual social and functional activities or pulse oximetry <90%), or life threatening. The PDWI definition was designed to be similar to definitions of medically significant wheezing used previously [6], and to include illness surpassing a severity threshold such that incidental wheezing illness without other significant signs or symptoms, such as dyspnea or tachypnea, was unlikely to be included.

The investigator determined the relationship between the study vaccine and adverse events as "related" or "not related". Events related to study vaccine were defined as temporally related to the administration of the study vaccine and no other etiology explained the event. For the purpose of this trial, temporally related was defined as being within one month of vaccination for PDWI and as being within one week of vaccination for all other adverse events.

2.7. Sample size determination

Two major considerations informed the sample size choice of 300 participants. First, this sample size was judged by the investigators to maximize close safety monitoring of the entire cohort while balancing logistical and feasibility concerns. Second, the sample size would allow suitable power to demonstrate significant differences in post-vaccination reactions which have been shown to be increased with FluMist® in the published literature (including fever and rhinorrhea), if they were to occur at rates similar to prior reports [6]. The trial was not designed to have statistical power to demonstrate significant differences in less common outcomes such as SAEs or medically significant wheeze, if they were to occur at rates similar to prior reports from larger trials [6].

2.8. Data analysis

All analyses and summaries were performed on a modified intention-to-treat basis: only data from those participants who received study vaccine/placebo were analyzed. Primary safety results were based on frequencies of participants who had or acquired the characteristics of interest, regardless of duration of follow up. Age categories were 24 through 35 months, 36 through 47 months, and 48 through 59 months. Categorical data were summarized by the number and percentage of participants within each category. Continuous variables, such as measured temperature and respiratory rate, were summarized according to threshold values and summarized as categorical data. Two-sided p values ≤ 0.05 were considered statistically significant. We made no multiplicity adjustment for safety endpoints. This was a conservative approach since not performing such an adjustment makes it less likely that a safety signal would be missed. For safety outcomes that may have occurred more than once for each particular participant, the participant was censored at the time to the first event (per time period analyzed). A priori analyses included comparisons of solicited and unsolicited events, PDWIs, and SAEs by vaccine group overall, as well as by severity grading and relationship among age groups and over different time periods post-vaccination (0–7 days, 8–42 days, 43 days through study end, or over the entire study period). Post hoc analyses included comparison of PDWI over the entire study period, by study clinic documentation of past bronchodilator treatment, as well as tachypnea identified at home and in the study clinic by vaccine groups, overall and by age grouping. Analyses were performed with SAS software (version.9.3; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Participant flow

A total of 309 children were enrolled in the study (Fig. 1). After enrollment, 9 children were found to meet study exclusion criteria, did not receive study vaccine, and were discontinued from further trial activities. Of the remaining children, 300 participants were randomized and administered LAIV (150) or placebo (150). Of the children who received study vaccine, 297 (99.0%) participants had weekly follow-up visits through study completion, and three (1.0%) participants migrated out of the study area but provided safety data until their departure.

3.2. Baseline characteristics

Children receiving LAIV and placebo were 24 through 35 months (25.3% vs. 20.7%), 36 through 47 months (38.7% vs. 38.0%), and 48 through 59 months of age (36.0% vs. 41.3%) at the time of vaccination (Table 1). 131 children had a parent report that they previously received medical treatment or been hospitalized for wheezing illness, with an equal percentage occurring in both study groups (43.3% vs. 44.0%).A minority of children had previously been hospitalized for wheezing illness (6.7% vs. 8.0%). One child with a history of hospitalization did not have a prior history of treatment for wheezing illness.

3.3. Solicited adverse events

There were no immediate post-vaccination reactions in either vaccine group. There were no statistically significant differences of participants with any solicited post-vaccination reactions between vaccine groups within the first 7 days post-vaccination (Table 2). Among the solicited reactions in this time period, LAIV recipients experienced 50 mild and 5 moderate events, while placebo recipients experienced 52 mild and 2 moderate events. There were no severe or life threatening solicited reactions. There were no imbalances in solicited reactions between the vaccine and placebo groups when analyzed by day during the first 7 days post-vaccination overall, by severity grading, or by age group (data not shown).

Though not a protocol-defined safety endpoint, solicited reactions were systematically collected through the end of the study. Through the 42 days post vaccination, as well as throughout the entire study period, there were no statistically significant differences in participants with solicited reactions. There was a non-significant imbalance in tachypnea occurring during the day 8–42 day period following vaccination ($n = 5$ LAIV vs. $n = 0$ placebo, $p = 0.06$). Tachypnea events were graded as present/absent only without further severity classification.

Given the imbalance in tachypnea between vaccine groups identified by FRAs in participant homes, we conducted a *post hoc* analysis of tachypnea assessed in the study clinic among participants referred by FRAs or self-referring (Supplemental Tables 1 and 2). We found no statistically significant differences in participants

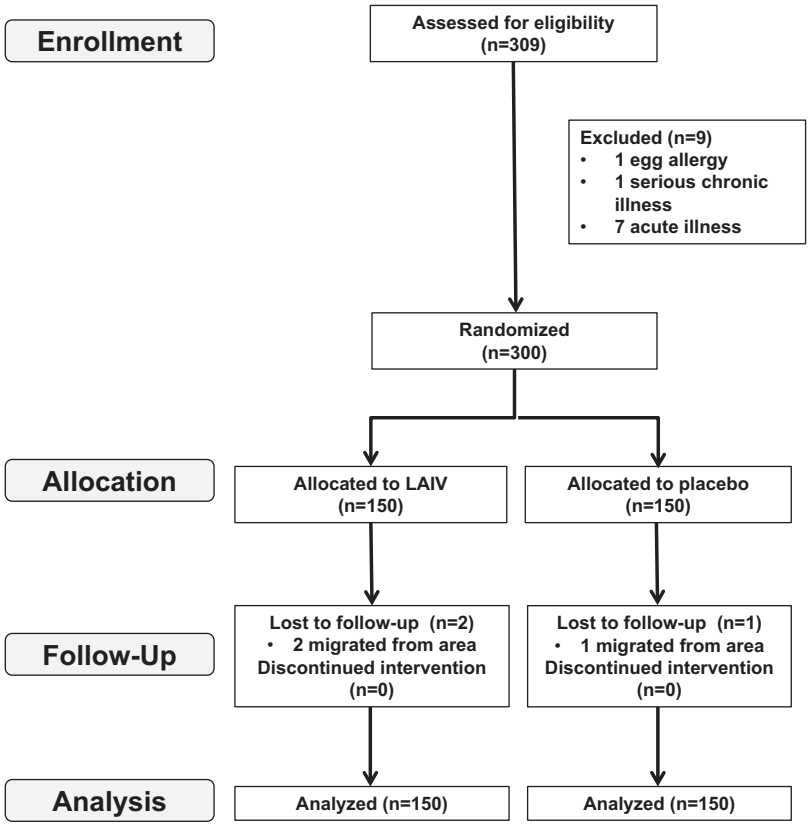

Fig. 1. Participant flow.

with tachypnea events as identified in the study clinic between the study groups during the first 7 days post-vaccination (2 LAIV vs. 5 placebo, $p = 0.448$). LAIV recipients, however, had significantly more tachypnea events identified in the study clinic compared to placebo recipients (14 LAIV vs. 3 placebo, $p = 0.010$) from days 8–42 post-vaccination. Most of these events occurred among children 24 through 35 months (8 LAIV and 1 in placebo, $p = 0.035$) and 48 through 59 months (4 LAIV and 0 in placebo, $p = 0.044$) of age. There were no statistically significant differences in participants with tachypnea between LAIV and placebo groups from days 43 through study end or over the entire study period among all ages or by age group. The number of children found to have tachypnea events in the study clinic that had PDWI during the first 7 days post-vaccination was 1 LAIV vs. 1 placebo, and the number with PDWI during days 8–42 days post-vaccination were 2 LAIV vs. 1 placebo.

3.4. Unsolicited adverse events

Among all unsolicited adverse events identified by FRAs in participant homes, there were statistically more participants

Table 1
Participant baseline data.

Characteristic (*n*, %)	LAIV (*n*, %)	Placebo (*n*, %)
Number of participants[a]	150 (100.0%)	150 (100.0%)
Age group		
24 through 35 months	38 (25.3%)	31 (20.7%)
36 through 47 months	58 (38.7%)	57 (38.0%)
48 through 59 months	54 (36.0%)	62 (41.3%)
Female	73 (48.7%)	66 (44.0%)
History of any asthma/wheezing therapy or hospitalization	65 (43.3%)	66 (44.0%)
History of any asthma/wheezing therapy	65 (43.3%)	65 (43.3%)
History of hospitalization with therapy for asthma/wheezing	10 (6.7%)	12 (8.0%)
Stunting[b]		
No	29 (19.3%)	39 (26.0%)
Mild	62 (41.3%)	59 (39.3%)
Moderate/severe	59 (39.4%)	52 (34.6%)
Concomitant medications[c]		
Antibacterial	1 (0.7%)	0 (0.0%)
Antipyretic	1 (0.7%)	4 (2.7%)
Other	5 (3.3%)	4 (2.7%)

[a] Seasonal influenza vaccine is not licensed, recommended or available to children in Bangladesh, and none of the enrolled children had prior influenza vaccine exposure.
[b] Mild stunting defined as height-for-age ≤ -1 and ≥ -2 SD and Moderate/Severe stunting defined as height-for-age < -2 or greater SD from the international reference median value (http://whqlibdoc.who.int/hq/1997/WHO_NUT_97.4.pdf).
[c] At the time of enrolment, three participants (2 placebo, 1 LAIV) were taking antihistamines for cough or runny noses, two participants (1 placebo, 1 LAIV) were taking homeopathic remedies, two participants (1 placebo, 1 LAIV) were taking antitussives, one participant (LAIV) was taking paracetamol for knee trauma, and one participant (LAIV) was taking an antimicrobial for giardiasis.

Table 2
Solicited adverse event by vaccine group in first 7 days post-vaccination.

Solicited adverse event	LAIV group (n = 150) n (%)	Placebo group (n = 150) n (%)	p-Value
Fever (measured ≥38.0)	5 (3.3%)	5 (3.3%)	1.000
Ear pain	2 (1.3%)	2 (1.3%)	1.000
Cough	10 (6.7%)	8 (5.3%)	0.809
Runny nose/nasal congestion	31 (20.7%)	34 (22.7%)	0.779
Sore throat	2 (1.3%)	0 (0.0%)	0.498
Headache	1 (0.7%)	0 (0.0%)	1.000
Irritability/decreased activity	0 (0.0%)	0 (0.0%)	–
Vomiting	2 (1.3%)	3 (2.0%)	1.000
Lethargy	0 (0.0%)	0 (0.0%)	–

Notes: (1) Events in this table were ascertained by daily Field Research Assistant (FRA) home visits. (2) All events were mild except for moderate events fever (2 LAIV vs. 1 placebo) and cough (3 LAIV vs. 1 placebo). There were no severe events.

with events among those who had received LAIV than placebo during the first 7 days post-vaccination (n = 20 vs. n = 8, p = 0.028), however there was no difference between groups from days 8–42 post-vaccination (37 vs. 27, p = 0.204), or from days 43 through study end (79 vs. 91, p = 0.200). Similar proportions of participants experienced moderate events between LAIV and placebo groups from days 0–7 post-vaccination (3.3% vs. 0.0%), days 8–42 post-vaccination (2.7% vs. 1.3%), and days 43 through study end (6.7% vs. 6.0%). Throughout the trial, there were similar numbers of LAIV (96) and placebo (94) participants who experienced unsolicited reactions. Specific unsolicited adverse events occurring throughout the trial are detailed in Table 3. Of these, LAIV and placebo participants experienced moderate events (11.3% vs. 6.7%) and mild events (52.7% and 56.0%).

3.5. Protocol-defined wheezing illness (PDWI)

PDWI events occurred throughout the trial (Fig. 2 and Supplemental Table 3). There were no statistically significant differences in participants experiencing PDWI between LAIV and placebo groups throughout the entire study (n = 13 vs. n = 16, p = 0.697). All PDWI events were of mild severity. There were 38 total clinic visits where PDWI was identified during the trial, with 6 participants having more than one clinic visit when PDWI was identified (Supplemental Table 3). Fifteen PDWI cases had positive laboratory tests for respiratory viruses (5 adenovirus, 7 respiratory syncytial virus, 3 human metapneumovirus), although none of the PDWI cases had influenza virus detected. In a *post hoc* analysis, we compared participants with PDWI events by age category and time period and there were no significant differences in events by vaccine group (data not shown). In a *post hoc* analysis, we compared participants with PDWI by study group among the subset of participants that had a history of treatment or hospitalization for asthma or wheezing illness at baseline, and there was no statistical differences in events occurring throughout the trial between LAIV and placebo groups (5 vs. 13, p = 0.074)

3.6. Serious adverse events

There were six SAEs (Supplemental Table 4). All six occurred among participants in the LAIV group. Three of the events resulted in hospitalization. All events were moderate in severity, all resolved, and none was judged to be related to study vaccine receipt. These SAEs included three due to traumatic injury and bone fracture, and one each due to accidental overdose of paracetamol, abdominal pain, and acute gastroenteritis. None of the participants with SAEs had wheezing illness or other signs of acute respiratory illness at the time of their events. All of the children with SAEs recovered.

4. Discussion

Russian-backbone LAIV has the potential to be effective, affordable, and logistically feasible for immunization of children in low-resource countries [17]. This randomized, placebo-controlled trial was the first to prospectively assess wheezing illness after receipt of a Russian-backbone LAIV. In this population of urban Bangladeshi children with a high prevalence of wheezing illness at baseline [18], LAIV was well tolerated, and we found no statistically significant differences in our primary safety endpoints: solicited adverse events during the first 7 days-post-vaccination or other adverse events occurring throughout the study, including unsolicited adverse events, PDWI, all cause hospitalizations, and SAEs related to study vaccination.

There were some event imbalances between treatment groups, including six SAEs in the LAIV group as compared to none in the placebo group. None of these SAEs had respiratory symptoms or were judged to be related to the vaccine. Post hoc analyses of

Table 3
Participants with unsolicited adverse events (any vs. none), by vaccine group over the entire study period.

Adverse event classification	LAIV group (n = 150) n (%)	Placebo group (n = 150) n (%)	2-sided Fisher's exact
Diarrheal illness	38 (25.3)	32 (21.3)	0.495
Oral thrush	26 (17.3)	18 (12.0)	0.253
Boil/abscess/skin infection/ulcer/cyst	11 (7.3)	18 (12.0)	0.241
Helminthiasis	9 (6.0)	11 (7.3)	0.818
Scabies	8 (5.3)	6 (4.0)	0.785
Abdominal pain/distension	5 (3.3)	6 (4.0)	1.000
Allergy	6 (4.0)	6 (4.0)	1.000
Fungal infection	6 (4.0)	5 (3.3)	1.000
Other	55 (36.7)	51 (34.0)	0.717

Notes: (1) All Day 0–7 events were mild with the exception of 2 moderate diarrhea events and 3 moderate "other" events (all traumatic injury) in the LAIV group. All placebo group events in the 0–7 day period were mild in severity. All Day 8 through study end events were mild except for moderate events diarrheal illness (3 LAIV vs.2 placebo), oral thrush (1 LAIV vs. 1 placebo), Boil/Abscess/Skin Infection/Ulcer/Cyst (2 LAIV vs. 0 placebo) abdominal pain/distension (1 LAIV vs.1 placebo), allergy (0 LAIV vs. 2 placebo) and other classifications (9 LAIV vs. 6 placebo). (2) There were no severe adverse events.

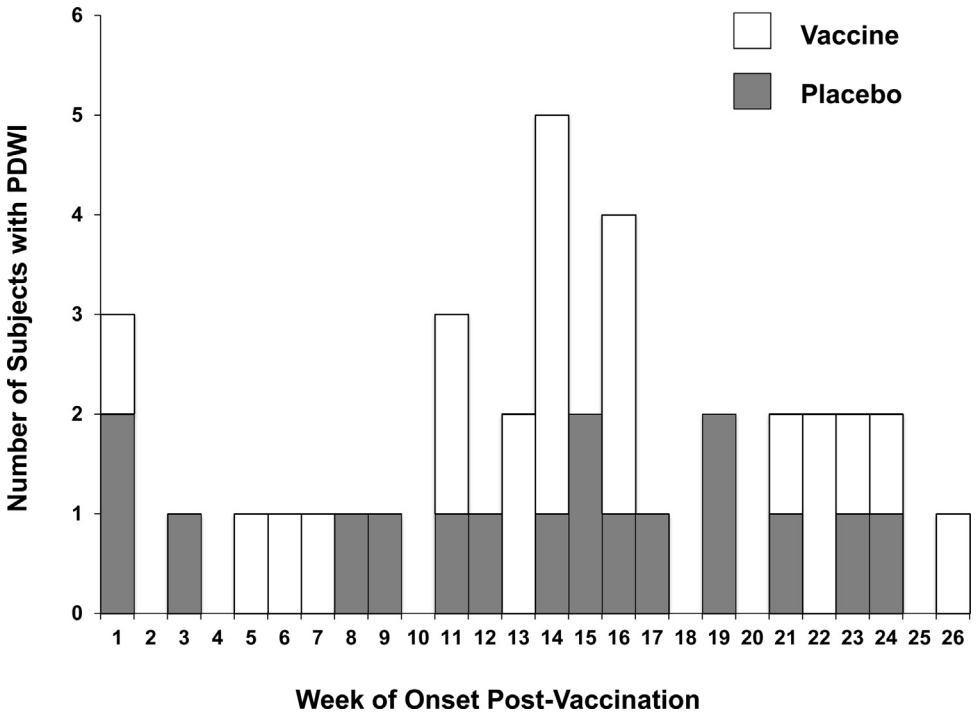

Fig. 2. Protocol-defined wheezing illness (PDWI) identified during illness visits by vaccine group. *Note*: Because some individuals had an adverse event coded more than once throughout the trial, total events summarized in the online supplement include more events than are included in the safety analyses, which only allow a single event to be counted per participant in each time period.

trial data found imbalances of tachypnea, defined as a respiratory rate ≥40 breaths/min, among two and four year old children but not among three year olds. While tachypnea can correlate with wheezing illness, a major safety endpoint for this trial, we found no imbalance in PDWI. While Russian-backbone LAIV had never been associated with wheezing illness, previous clinical trials of the vaccine did not prospectively solicit this event and included few children younger than 24 months of age (the age group at risk for wheezing in FluMist® trials) [6,19]. Larger studies with robust safety evaluations will be necessary to better determine whether tachypnea or wheezing illness is also a safety concern in young children receiving the Russian-backbone LAIV.

This trial should be interpreted in the context of its limitations. The background rates of previous wheezing illness in these children are higher than previous estimates from other developing countries and may affect the generalizability of the safety results from this single center study [20]. Children with wheezing illness who did not seek care at the study clinic or who did not meet the referral criteria threshold upon seeking care in the clinic would not have been captured by our safety surveillance. However, referral criteria were sensitive, and would likely have missed few medically important adverse events. While we found no imbalances in PDWI or related SAEs between vaccine groups, the study was not powered to detect significant differences in rare events. Finally, while we did find imbalances in tachypnea among children two and four years of age, these were not a priori analyses, participant denominators were small, and we did not adjust analyses for multiple comparisons. This finding should be interpreted with caution.

PATH is currently sponsoring two safety and efficacy trials using the SIIL LAIV among children in Bangladesh and Senegal [21,22]. These larger trials with 1761 participants each will better assess the risk of less common safety outcomes associated with vaccine receipt among pediatric age groups. Likewise, these efficacy trials will allow risk-benefit assessments to inform vaccine policy in Bangladesh, Senegal, and other countries with high attack rates of pediatric influenza [13,23].

Disclaimer

The findings and conclusions in this report are those of the authors. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of their organizations.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.04.048

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