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Original Article

Immunogenicity of a quadrivalent Ann Arbor strain live attenuated influenza vaccine delivered using a blow-fill-seal device in adults: a randomized, active-controlled study*

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Background Influenza B strains from two distinct lineages (Yamagata and Victoria) have cocirculated over recent years. Current seasonal vaccines contain a single B lineage resulting in frequent mismatches between the vaccine strain and the circulating strain. An Ann Arbor strain quadrivalent live attenuated influenza vaccine (Q/LAIV) containing B strains from both lineages is being developed to address this issue.

Objectives The goal of this study was to evaluate whether Q/LAIV administered intranasally as a single dose to a single nostril, using a blow-fill-seal (BFS) delivery system had a similar immunogenicity and safety profile compared with the licensed trivalent vaccine delivered using the Accuspray device.

Patients/Methods Adults aged 18–49 years were randomized to receive one intranasal dose of Q/LAIV delivered using a BFS device (Q/LAIV-BFS; $n = 1202$) or one of two trivalent live attenuated influenza vaccines (T/LAIV) containing one of the corresponding B strains (total T/LAIV, $n = 598$). Primary endpoints were the post-vaccination strain-specific serum hemagglutination inhibition antibody geometric mean titers for each strain. Secondary immunogenicity endpoints, safety, and acceptability of the BFS device were also assessed.

Results Q/LAIV was immunogenically non-inferior to T/LAIV for all four influenza strains. Secondary immunogenicity outcomes were consistent with the primary endpoint. Solicited symptoms and AEs were comparable in both groups. Subjects considered the BFS device to be acceptable.

Conclusions Immune responses to vaccination with Ann Arbor strain Q/LAIV-BFS were non-inferior to those with T/LAIV. Q/LAIV may confer broader protection against seasonal influenza B by targeting both major influenza B lineages.

Keywords Immunogenicity, intranasal drug administration, live attenuated influenza vaccine, quadrivalent.

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Introduction

Annual vaccination is the most effective method for preventing illness and complications related to infection with influenza.[1,2] Licensed seasonal influenza vaccines contain one strain each of influenza A/H1N1, A/H3N2, and B viruses, with annual strain selection based on predictions of which strains will ultimately circulate.[2,3]

Although influenza B may be more genetically stable than influenza A, the dominant circulating B strain typically varies from season to season.[4–12] Over the past three decades, two distinct antigenic lineages, B/Yamagata and B/Victoria, have emerged, with limited to no immunologic crossreactivity across lineages.[13,14] Predicting which of the two lineages will predominate in the upcoming season has been difficult, and the correct B lineage virus has only been

included in seasonal influenza vaccines in approximately half of the past 10 years.[15–18]

Over the past 10 influenza seasons in the United States, the annual proportion of all influenza strains identified as type B varied from 1% to 46%; the proportion of circulating B strains not matched to the vaccine strain varied from 0% to 98%.[19] During the 2007–2008 influenza season, approximately 29% of all circulating strains were B lineage; 98% of those were from the lineage not contained in the vaccine.[19] Similar rates of B viruses circulated in Europe during the 1999–2007 influenza seasons (1–48% of all strains).[20] A US Centers for Disease Control and Prevention model projected that the use of a quadrivalent vaccine during the 2007–2008 season would have decreased influenza cases by 1·1 million and hospitalizations by 7488.[18] Support for expanding the annual influenza vaccine to contain four strains (including a representative from each B lineage) has increased.[21]

A trivalent Ann Arbor strain live attenuated influenza vaccine (T/LAIV; MedImmune, LLC, Gaithersburg, MD, USA) is currently approved for use in a number of countries (including the United States for eligible individuals 2–49 years of age). The vaccine is administered as a half-dose to each nostril using an Accuspray delivery device (Becton Dickinson, Franklin Lakes, NJ, USA). An investigational quadrivalent Ann Arbor strain live attenuated influenza vaccine (Q/LAIV) has been produced using processes identical to those used for T/LAIV, with the exception that four attenuated virus strains (influenza A/H1N1 and A/H3N2, and two influenza B viruses, one each from the Yamagata and Victoria lineages) are combined in the vaccine. The immunogenicity, safety, and tolerability of Q/LAIV were initially evaluated in adults with the vaccine administered using the Accuspray delivery device (Figure 1A); the immunogenicity and safety profile of Q/LAIV were found to be comparable with T/LAIV.[22] In this study, Q/LAIV was administered intranasally as one dose to one nostril, using a blow-fill-seal (BFS) delivery system (Figure 1B). BFS systems are used for a variety of prescription medicines and many over-the-counter medications. In these systems, a plastic container is formed, filled, and sealed sterilely. Potential benefits of the BFS system for intranasal vaccine administration include a high level of assurance of aseptic processing, ease of administration, facilitated packaging and distribution, and lower overall cost.

The goal of this study was to evaluate whether Q/LAIV delivered by BFS (Q/LAIV-BFS) had a similar immunogenicity and safety profile compared with T/LAIV delivered using the Accuspray device. Immune responses induced by Q/LAIV-BFS were compared with those elicited by T/LAIV by using post-vaccination strain-specific serum hemagglutination inhibition antibody (HAI) geometric mean titers (GMTs).

Methods

Study design

This randomized, partially blind, active-controlled, phase 2/3 study in subjects 18–49 years of age was conducted from August 14, 2009 to March 3, 2010 at 18 clinical sites in the United States. Vaccination and blood collection for immunogenicity testing occurred during the influenza off-season. Because of visual differences between the BFS and Accuspray devices, subjects and designated on-site dose administrators were not blinded; all other personnel involved with the conduct and analysis of the study, including laboratory staff, remained blinded throughout the study. Subjects were randomized using an interactive voice response system in a 4:1:1 ratio to receive one dose of Q/LAIV-BFS or T/LAIV containing an influenza B strain of Ann Arbor vaccine virus derived from the B/Yamagata or the B/Victoria lineages (T/LAIV-B/Yamagata or T/LAIV-B/Victoria, respectively); randomization was stratified by site. The primary objective of this study was to evaluate the immunologic responses to Q/LAIV-BFS compared with the two formulations of T/LAIV using post-vaccination strain-specific GMTs. Secondary endpoints

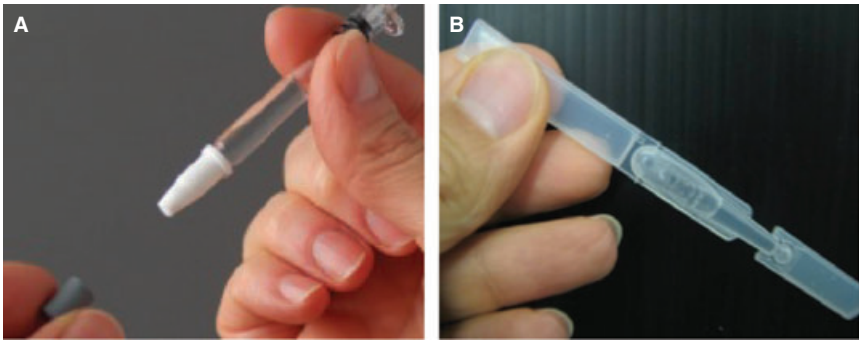

Figure 1. Photograph of (A) accuspray delivery device and (B) blow-fill-seal delivery system.

assessed included the rate of seroconversion/seroresponse (≥4-fold increase in HAI titers from baseline), safety of Q/LAIV-BFS, and acceptability of the BFS vaccine delivery system. This study (Clinicaltrials.gov identifier NCT00952705) was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guidance for Good Clinical Practice, and any conditions required by a regulatory authority and/or institutional review board/independent ethics committee.[23] Written informed consent was obtained from each subject before conduct of any protocol-specific activity.

Study participants

Subjects with chronic illness with no illness-related hospitalization the previous year or change in medication dose level within 90 days before randomization were permitted to enroll, per investigator judgment. Subjects with active illness (or fever ≥38°C) and those receiving blood products or immunoglobulin within 90 days before randomization, investigational drugs, any non-study vaccine, or antiviral agents with activity against influenza within 30 days before study vaccination were excluded. Pregnant or lactating women and subjects with a history of Guillain-Barré syndrome or asthma, immunosuppression, or any condition that would interfere with evaluation of the study treatments were also excluded.

Analysis populations

The intent-to-treat population included all randomized subjects. The immunogenicity population included subjects who were vaccinated, had post-vaccination HAI measurements, and had no major protocol violations that interfered with immunogenicity assessment. Subjects were classified at baseline as serosusceptible (HAI antibody titer ≤8) or seropositive (HAI antibody titer >8). The safety population included vaccinated subjects for whom any follow-up safety data were recorded.

Study vaccine

All vaccines contained $10^{7.0 \pm 0.5}$ fluorescent focus units of each Ann Arbor viral strain delivered intranasally using the BFS delivery system (Q/LAIV-BFS; 0·2 ml, one nostril) or the Accuspray device (T/LAIV; 0·2 ml total, 0·1 ml per nostril). Q/LAIV was composed of four influenza strains: A/South Dakota/6/2007 (A/H1N1), A/Uruguay/716/2007 (A/H3N2), B/Malaysia/2506/2004 (B/Victoria), and B/Florida/4/2006 (B/Yamagata). T/LAIV preparations contained identical A strains but only one influenza B strain each, corresponding to the B strains in Q/LAIV-BFS.

Immunologic evaluations

Blood samples for HAI analysis were collected on day 0 pre-vaccination and once 28–35 days post-vaccination. Immunogenicity assays were conducted as previously described.[24,25] HAI testing was performed by MedImmune; HAI titers were determined as the reciprocal of the last serum dilution that gave complete inhibition of hemagglutination.

Safety

Solicited symptoms were collected daily on days 0–14. All reported adverse events (AE) were collected 0–28 days post-vaccination and were coded using the Medical Dictionary for Regulatory Activities version 12·0 (MedDRA, http://www.meddramsso.com). Serious adverse events (SAEs) and new-onset chronic diseases were collected through day 180 post-vaccination.

Dose delivery evaluations

Dosing from each device was assessed by site vaccine administrators to determine whether a full dose was delivered. Each subject was asked to complete a questionnaire, within 15 minutes post-vaccination, regarding their impression of the method of dose delivery. The questionnaire was developed through focus groups of adults that were shown delivery devices similar to those used in the study to identify issues associated with intranasal vaccination using BFS and Accuspray. The questionnaire concepts were further refined through a literature review of developed surveys regarding nasal delivery devices. Question wording was revised through a Delphi process.[26]

The questionnaire contained 16 primary questions in four areas: previous influenza vaccination experience, concern with intranasal delivery device (pre- and post-vaccination), overall satisfaction with the device, including delivery system preference for future influenza vaccinations, and perception of intranasal administration sensory attributes (sneezing, choking, gagging, coughing, taste, aftertaste, smell, pain or discomfort, and the sensation of vaccine running down the back of the throat or out the nose). For the sensory attributes, a follow-up question regarding the level of "bothersomeness" was asked of subjects who indicated a negative experience.

Statistical analysis

A sample size of 1800 subjects randomized 4:1:1 to Q/LAIV-BFS, T/LAIV-B/Yamagata, and T/LAIV-B/Victoria provided approximately 99·9% power for the A/H1N1 and A/H3N2 strains and 98·9% power for each of the B strains to demonstrate the non-inferior immunogenicity of Q/LAIV-BFS compared with T/LAIV (measured by post-vaccination GMT ratios), regardless of baseline serostatus. These calculations assumed a conservative 90% evaluability rate, a true post-vaccination GMT ratio for serum HAI of 1, and a SD of the natural logarithm-transformed HAI titer of 1·4 for all four strains. Study dropouts were not

replaced. A value of 2 was assigned for HAI titers reported as <4.

Geometric mean titers for the strain-specific influenza antigen measurements were defined as GMT = antilog (mean [log x]), where x was the strain-specific HAI titer. CIs were constructed using a percentile-based bootstrap method. The immune response of Q/LAIV-BFS was declared non-inferior to that of T/LAIV if the upper bound for each of the four 95% CIs for post-vaccination strain-specific GMT ratios (T/LAIV divided by Q/LAIV) was ≤1·5. Immunologic non-inferiority was evaluated against the combined T/LAIV groups for A/H1N1 and A/H3N2 strains and against T/LAIV-B/Yamagata and T/LAIV-B/Victoria separately.

The secondary immune response endpoints (the proportion of subjects who experienced a post-vaccination strain-specific HAI antibody seroresponse by baseline serostatus, and the proportion of subjects who achieved a strain-specific HAI titer ≥32 by baseline serostatus) were evaluated with 2-sided Clopper–Pearson 95% CIs. Test-based asymptotic 2-sided 95% CIs were constructed for the proportion differences (Q/LAIV-BFS minus comparator) using the standardized statistic (assuming an asymptotically normal distribution). Tabular summaries were provided for each treatment group and for the combined T/LAIV groups for the safety endpoints. No formal statistical comparisons were performed for safety summaries. Response rates were summarized for the subject questionnaire.

Results

Study population

Of the 1800 randomized adults, 1199 subjects received Q/LAIV-BFS, 300 subjects received T/LAIV-B/Yamagata, and 298 subjects received T/LAIV-B/Victoria; three subjects randomized to Q/LAIV-BFS were not vaccinated (two subjects withdrew consent; one subject failed to meet ongoing eligibility criteria). A total of 1747 (97·1%) subjects completed the study (Figure S1). There were 1762 and 1794 subjects in the immunogenicity and safety populations, respectively. The mean age of study participants was 33·9 years and demographics were well-balanced across treatment groups (Table 1).

Immune responses

Primary endpoint

Pre-vaccination HAI GMTs were similar for Q/LAIV and T/LAIV recipients, although slightly higher in the Q/LAIV-BFS group (Figure S2). For all subjects, the baseline GMTs were higher for the two B strains (B/Yamagata and B/Victoria) than for the A strains (A/H1N1 and A/H3N2). The study met its primary objective and demonstrated immunologic non-inferiority of Q/LAIV-BFS compared with two formulations of T/LAIV. The upper bound for each of the four 95% CIs for post-vaccination strain-specific GMT ratios (T/LAIV comparator group ÷ Q/LAIV-BFS) was less than the pre-specified margin of 1·5 (Table 2). Post hoc

Table 1. Demographic characteristics

Category	Q/LAIV-BFS (n = 1202)	T/LAIV (n = 598)*	T/LAIV-B/Yamagata (n = 300)	T/LAIV-B/Victoria (n = 298)	Total (n = 1800)
Age, years (SD)					
Mean	33·9 (9·5)	33·9 (9·0)	34·0 (9·1)	33·8 (8·8)	33·9 (9·3)
Median	34·0	34·0	34·0	33·0	34·0
Sex, *n* (%)					
Male	501 (41·7)	262 (43·8)	131 (43·7)	131 (44·0)	763 (42·4)
Ethnicity, *n* (%)					
Hispanic/Latino	149 (12·4)	81 (13·5)	35 (11·7)	46 (15·4)	230 (12·8)
Race, *n* (%)					
White	811 (67·5)	403 (67·4)	201 (67·0)	202 (67·8)	1214 (67·4)
Black/African American	351 (29·2)	158 (26·4)	83 (27·7)	75 (25·2)	509 (28·3)
Asian	10 (0·8)	13 (2·2)	7 (2·3)	6 (2·0)	23 (1·3)
American Indian/Alaskan Native	9 (0·7)	3 (0·5)	1 (0·3)	2 (0·7)	12 (0·7)
Native Hawaiian/Pacific Islander	1 (0·1)	3 (0·5)	1 (0·3)	2 (0·7)	4 (0·2)
Multiracial	10 (0·8)	8 (1·3)	3 (1·0)	5 (1·7)	18 (1·0)
Other	10 (0·8)	10 (1·7)	4 (1·3)	6 (2·0)	20 (1·1)

Q/LAIV-BFS = quadrivalent live attenuated influenza vaccine delivered using blow-fill-seal delivery system; T/LAIV = trivalent live attenuated influenza vaccine.
*Data from the T/LAIV-B/Yamagata and T/LAIV-B/Victoria arms combined.

Table 2. Geometric mean titer ratios 28 days post-vaccination

Strain	Q/LAIV-BFS		T/LAIV comparator*		GMT ratio (95% CI)
	n	GMT	*n*	GMT	
A/H1N1	1176	8·1	586	7·7	0·95 (0·87, 1·03)
A/H3N2	1176	8·3	586	7·7	0·93 (0·85, 1·00)
B/Yamagata	1176	60·3	294	54·1	0·90 (0·79, 1·02)
B/Victoria	1176	27·4	292	26·7	0·97 (0·87, 1·10)

GMT = geometric mean titer; Q/LAIV-BFS = quadrivalent live attenuated influenza vaccine delivered using blow-fill-seal delivery system; T/LAIV = trivalent live attenuated influenza vaccine.
*Data from T/LAIV-B/Yamagata and T/LAIV-B/Victoria combined for influenza A strains, from T/LAIV-B/Yamagata for B/Yamagata, and from T/LAIV-B/Victoria for B/Victoria.

analyses of geometric mean fold rises (GMFRs) in antibody titers, conducted to account for the slight differences in baseline GMTs between treatment groups, gave similar results—each of the four post-vaccination ratios were close to 1 (range, 0·98–1·07) and none of the 95% CIs exceeded 1·5 (comparator ÷ Q/LAIV-BFS).

Seroresponse rates

Distributions of subjects' baseline serostatus, by strain, are presented as the denominators in Table S1. For all subjects, regardless of baseline serostatus, the HAI seroconversion rates for the A/H1N1 strain were comparable (Q/LAIV-BFS,5·4%; T/LAIV, 6·5%). The seroconversion rates for the A/H3N2 strain were similar between the two treatment groups (Q/LAIV-BFS, 4·7%; T/LAIV, 4·8%). For both B strains, the seroconversion rates were slightly lower among Q/LAIV-BFS recipients compared with the matching T/LAIV groups (B/Yamagata: Q/LAIV-BFS, 8·2%; T/LAIV, 9·5%; B/Victoria: Q/LAIV-BFS, 7·5%; T/LAIV, 10·3%; Figure 2A).

Among serosusceptible subjects, seroconversion rates for the A strains were higher than those observed among all subjects, but similar when comparing the Q/LAIV-BFS and T/LAIV groups. The seroconversion rates to B/Yamagata in subjects who were serosusceptible at baseline were similar (Q/LAIV-BFS, 36·0; T/LAIV-B/Yamagata, 35·3%). For B/Victoria, the seroconversion rate was lower among Q/LAIV-BFS recipients (20·8%) than T/LAIV-B/Victoria recipients (26·0%, not statistically significant; Figure 2B).

Proportion of subjects achieving HAI antibody titers ≥32

In general, for all treatment groups, the proportions of subjects achieving titers ≥32 were higher for the B strains than the A strains and higher in all subjects than in serosusceptible subjects (Table S1). Absolute rate differences in the proportion of subjects achieving titers of ≥32 were all <4%; none were statistically significant.

Safety

Solicited symptoms

The percentage of subjects reporting ≥1 solicited symptom was similar among Q/LAIV-BFS and T/LAIV recipients (Q/LAIV-BFS, 50·6%; T/LAIV, 54·3%; Figure 3). Symptoms with rate differences ≥1% higher among Q/LAIV-BFS recipients included sore throat (2·3%; Q/LAIV-BFS, 17·3%; T/LAIV, 15·0%) and cough (1·7%; Q/LAIV-BFS, 9·6%; T/LAIV, 7·9%). Fewer Q/LAIV-BFS recipients than T/LAIV recipients reported runny/stuffy nose (−6·4%) and generalized muscle aches (−2·6%). The median number of days for which a solicited symptom was reported was similar across treatment groups (3·0 days).

Adverse events and new-onset chronic diseases

Adverse event rates experienced by both groups were similar (Q/LAIV-BFS, 15·6%; T/LAIV, 14·9%). No AE occurred with an absolute rate difference of more than ±1·0% point between Q/LAIV-BFS and T/LAIV recipients. The AEs among Q/LAIV-BFS recipients for which the rate differences were highest were headache (rate difference, 0·8%), cough (rate difference, 0·7%), and back pain (rate difference, 0·6%); all were similar to rates in T/LAIV recipients.

Four Q/LAIV-BFS recipients experienced four SAEs with onset within 28 days post-vaccination; none of these events were considered related to investigational product. Among these, one subject died 44 days post-vaccination of complications from cholecystitis, sepsis, and multiorgan failure, and one subject died 52 days post-vaccination from bilateral pneumonia and acute renal failure. Neither death was considered related to investigational product. The other events included ventricular wall aneurysm discovered during workup initiated before the study, and status asthmaticus occurring 22 days post-vaccination in a subject with an undisclosed history of asthma. Neither event was considered related to the study.

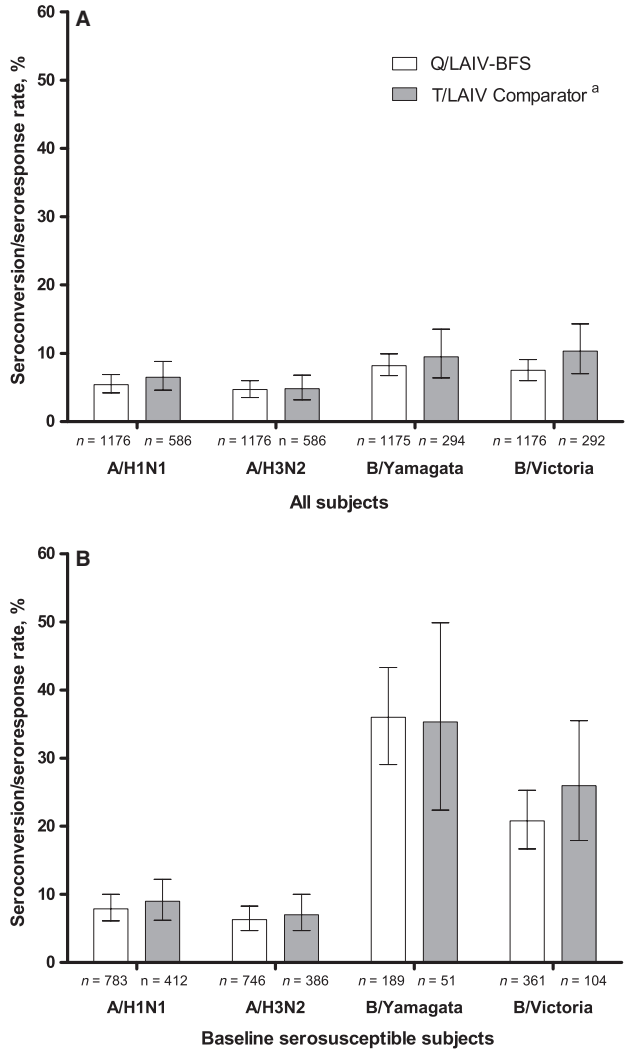

Figure 2. The percentage of subjects exhibiting a seroconversion/seroresponse, defined as a fourfold rise in hemagglutination inhibition (HAI) titer from baseline, by strain 28 days post-vaccination. (A) All subjects. (B) Serosusceptible subjects. [a]Data from T/LAIV-B/Yamagata and T/LAIV-B/Victoria combined for influenza A strains, from T/LAIV-B/Yamagata for B/Yamagata, and from T/LAIV-B/Victoria for B/Victoria. Q/LAIV-BFS = quadrivalent live attenuated influenza vaccine delivered using blow-fill-seal delivery system; T/LAIV = trivalent live attenuated influenza vaccine.

Fifteen Q/LAIV-BFS recipients (1·3%) experienced 18 SAEs 0–180 days post-vaccination, and two T/LAIV recipients (0·3%) experienced four SAEs 0–180 days post-vaccination. One subject experienced a miscarriage 33 days post-vaccination with Q/LAIV-BFS. The pregnancy was undocumented at enrollment due to a false-negative urine pregnancy test. This SAE was assessed by the investigator as possibly related to investigational product and was assessed by the Independent Safety Monitoring Committee overseeing the study as unrelated to investigational product. All other SAEs were assessed to be unrelated to investigational product. Six Q/LAIV-BFS (0·5%) and three T/LAIV (0·5%) recipients experienced one new-onset chronic disease each within 180 days post-vaccination; all were considered unrelated to investigational product.

Method of dose delivery

Study personnel who administered vaccine to subjects assessed the ease of vaccine delivery for each device and whether each dose of vaccine was delivered completely. The percentage of subjects receiving the entire dose of Q/LAIV via the BFS delivery system was 98·7% compared with 99·3% of subjects receiving T/LAIV delivered using the Accuspray device. Eight of the 18 sites in the study reported difficulties properly opening the BFS system, involving approximately 4% of devices.

A majority of subjects reported receipt of influenza vaccination during a previous influenza season (Q/LAIV-BFS, 65·8%; T/LAIV, 63·9%); >97% of whom reported previous vaccination by injection. Most subjects reported no concerns regarding the delivery device before (Q/LAIV-BFS, 83·3%; T/LAIV, 84·4%) or after (Q/LAIV-BFS, 94·0%; T/LAIV, 96·1%) vaccination.

With exception of two sensory attributes, the majority of subjects in both groups (>80%) reported not experiencing the specific solicited sensory attributes. The experience of vaccine running down the back of their throat (Q/LAIV-BFS, 73·3%; T/LAIV, 63·3%) was considered "slightly" or "not at all" bothersome (Q/LAIV-BFS, 89·7%; T/LAIV, 90·7%); vaccine running out of the nose (Q/LAIV-BFS, 28·2%; T/LAIV, 35·1%) was also considered "slightly" or "not at all" bothersome (Q/LAIV-BFS, 92·4%; T/LAIV, 92·8%).

Recipients generally reported being very satisfied or satisfied with the vaccine device used (Q/LAIV-BFS, 86·1%; T/LAIV, 90·0%). Intranasal delivery was preferred if given the option between intranasal or injectable vaccination (Q/LAIV-BFS, 87·8%; T/LAIV, 88·3%). Subjects also reported that they would be "very likely" or "likely" to select the same device for their next influenza vaccination (Q/LAIV-BFS, 84·4%; T/LAIV, 86·4%).

Discussion

In this study, Q/LAIV-BFS was compared with trivalent vaccine formulations administered using Accuspray devices. The goal of the study was to evaluate how the new formulation and delivery system compared with the currently approved live influenza vaccine for which extensive safety, immunogenicity, and efficacy data exist. The study demonstrated that the immunogenicity of the quadrivalent formulation, delivered as a single intranasal dose, was non-inferior to the immunogenicity of a trivalent vaccine delivered as a half-dose to each nostril, with comparable

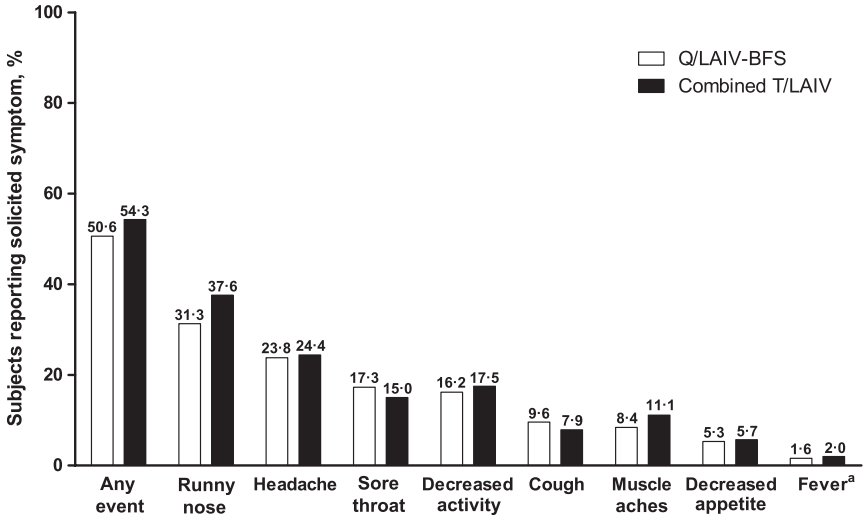

Figure 3. Subjects with solicited symptoms within 14 days post-vaccination. Q/LAIV-BFS = quadrivalent live attenuated influenza vaccine delivered using blow-fill-seal delivery system; T/LAIV = trivalent live attenuated influenza vaccine. [a]Temperature >38°C.

safety profiles for the two vaccine formulations. Secondary immunogenicity outcomes supported the conclusions of the primary analysis. Overall HAI responses seen in adults in both arms of the study were modest but similar to responses previously observed in adults after immunization with live attenuated influenza vaccines.[27,28] Live attenuated Ann Arbor strain vaccines that induce modest HAI responses in adults have been shown to afford significant protection against influenza illness, demonstrating that these serum antibody responses are not absolute correlates of protection. For example, in a T/LAIV challenge study, the estimated protective efficacy of the vaccine against laboratory documented influenza illness was 85% although the overall HAI seroconversion rate in serosusceptible subjects was 20%.[27]

In this study, the addition of a fourth strain and delivery via the BFS system did not appear to increase the reactogenicity of the vaccine because the proportion of subjects experiencing solicited symptoms and AEs was comparable between Q/LAIV-BFS and T/LAIV recipients, and the events observed were consistent with those previously observed in studies of T/LAIV[29–37] and Q/LAIV.[22] Although a higher proportion of Q/LAIV-BFS recipients reported SAEs from day 0–180 post-vaccination (1·3% versus 0·3%) and two SAEs resulted in deaths, all events, with one exception, were considered unrelated to investigational product. After review by the study team and the Independent Safety Monitoring Committee, the imbalance was not considered to represent a difference in the safety profile of the two vaccine formulations because the majority of events lacked a temporal or biological association with vaccination.

Difficulties reported in opening approximately 4% of the BFS units did not affect the results of the study; the safety and immunogenicity results between the Q/LAIV-BFS and the combined T/LAIV groups were comparable. However, the BFS opening failure rate has led to a reassessment of this delivery system. Overall satisfaction levels with vaccine delivery were comparable between groups.

A limitation of this study is that the assessment of immunologic non-inferiority was based on HAI antibody results and did not include other aspects of the immune response to the live vaccines. The HAI GMT ratio was selected as the primary endpoint for the study based on published guidance[38] and after consultation with the US Food and Drug Administration. Although HAI responses are not an absolute correlate of protection for live attenuated influenza vaccines, they are an indicator of a strain-specific functional immune response to vaccination and, when present, do correlate with protection against influenza.[29,30,33,39]

This study demonstrated that a quadrivalent Ann Arbor strain live attenuated influenza vaccine delivered via the BFS system had an immunogenicity profile in adults that was comparable with two trivalent formulations. The safety profiles of both formulations were similar, and the addition of a fourth strain to the vaccine did not result in any new safety signals being detected. Although the delivery system evaluated in the study did not perform at a satisfactory level, administration of Q/LAIV as a single dose to one nostril did not significantly alter the safety or immunogenicity profile of the vaccine. Given the frequent mismatches between circulating influenza strains and those selected annually for inclusion in the vaccines, a quadrivalent vaccine containing influenza B strains from the B/Victoria and the B/Yamagata lineages may provide an overall public health benefit.

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Conflicts of interest

EAS and RJ received research funding from MedImmune to conduct this study. JAS, SC, and MDR were employees of MedImmune at the time this study was conducted. FD and RMM are employees of MedImmune, LLC.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. CONSORT diagram; subject disposition.

Figure S2. Geometric mean titer by strain, day 0.

Table S1. Postvaccination strain-specific HAI antibody titer ≥32 by baseline serostatus.

Data S1. Study investigators.