Self-administration of intranasal influenza vaccine: immunogenicity and volunteer acceptance

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ABSTRACT

Background

In outbreak settings, mass vaccination strategies could maximize health protection of military personnel. Self-administration of live attenuated influenza vaccine (LAIV) may be a means to vaccinate large numbers of people and achieve deployment readiness while sparing the use of human resources.

Methods

A phase IV, open-label, randomized controlled trial evaluating the immunogenicity and acceptance of self-administered (SA) LAIV was conducted from 2012-2014. SA subjects were randomized to either individual self-administration or self-administration in a group setting. Control randomized subjects received healthcare worker-administered (HCWA) LAIV. Anti-hemagglutinin (HAI) antibody concentrations were measured pre- and post-vaccination. The primary endpoint was immunogenicity non-inferiority between SA and HCWA groups. Subjects were surveyed on preferred administration method.

Results

A total of 1077 subjects consented and were randomized (529 SA, 548 HCWA). Subject characteristics were very similar between groups, though SA subjects were younger, more likely to be white and on active duty. The per-protocol analysis included 1024 subjects (501 SA, 523 HCWA). Post-vaccination geometric mean titers by vaccine strain and by study group (HCWA vs. SA) were: A/H1N1 (45.8 vs. 48.7, respectively; $p=0.43$),

A/H3N2 (45.5 vs. 46.4; $p=0.80$), B/Yamagata (17.2 vs. 17.8; $p=0.55$). Seroresponses to A components were high (~67%), while seroresponses to B components were lower (~25%). Seroresponse did not differ by administration method. Baseline preference for administration method was similar between groups, with the majority in each group expressing no preference. At follow-up, the majority (64%) of SA subjects preferred SA vaccine.

Conclusions

LAIV immunogenicity was similar for HCWA and SA vaccines. SA was well-tolerated and preferred to HCWA among those who performed SA.

INTRODUCTION

The vaccination of large numbers of people within a limited period of time (mass vaccination) has been an important strategy for the control and prevention of several infectious diseases, including smallpox, polio, measles and meningococcal disease. Mass vaccination can be employed as a means to: [1] control outbreaks, [2] provide immunization services to populations without ready access to them, [3] immunize groups of people arriving at a specific place in a short interval of time or on a recurring basis, or [4] introduce a new vaccine or implement a new immunization policy [1].

Military personnel in congregate settings are at increased risk for infectious diseases, and acute respiratory infections (ARI) are among the most common [2, 3]. Influenza is a major cause of ARI and annual influenza vaccination is a requirement for US military personnel. In the event of an influenza outbreak or pandemic, a rapidly deployed mass vaccination strategy would maximize health protection of military personnel. Self-administration of live attenuated influenza vaccine (LAIV) may be a means to achieve deployment readiness while sparing the use of human resources, particularly health care personnel, in emergency situations. Herein we describe the results of a phase IV, open-label randomized controlled trial with an immunogenicity endpoint to assess the feasibility and acceptance of self-administration of influenza vaccine in a military setting.

METHODS

We conducted a phase IV, open-label, randomized controlled trial to assess whether the immunogenicity of self-administered LAIV (SA-LAIV) is non-inferior to that of health care

worker-administered LAIV (HCWA-LAIV). We also evaluated the feasibility of self-administration for individuals organized into groups and receiving instructions from a single health care worker.

Volunteers were recruited from US Department of Defense (DoD) beneficiary populations at the San Antonio Military Medical Center and the Naval Medical Center San Diego. Healthy males and healthy, non-pregnant females, aged 18 to 49 years, who were active duty military personnel or DoD beneficiaries, able to speak and understand English, and provide written informed consent were eligible to participate. The following individuals were excluded: those with known hypersensitivity to eggs or egg-proteins, or who have had adverse reactions to previous influenza vaccination; those who had already received influenza vaccine for the season of recruitment; those with known clinical diagnosis of reactive airway disease, wheezing, or asthma; those with reported febrile upper respiratory illness ($>100^{\circ}\text{F}$ or a subjective fever) at the time of or within the 24 hours prior to immunization; those with immunocompromising illnesses; and those who were trained to administer or who had been involved with the administration of intranasal vaccines previously.

Subjects were randomized into one of two treatment arms: HCWA-LAIV and SA-LAIV. Subjects in the SA-LAIV arm were further randomized to either individual self-administration, or self-administration in a group setting (groups of 5 or groups of 10). All vaccinations in the SA-LAIV arm were given under the direction and supervision of a research staff member who was trained to administer LAIV vaccines. Serum was

collected prior to vaccination and 28 (± 7) days post-vaccination for evaluation of anti-hemagglutinin antibody.

Intranasal live attenuated influenza vaccine (FluMist[®]) was manufactured by MedImmune (Gaithersburg, MD) and was provided as a 0.2 mL suspension in a single-dose pre-filled intranasal sprayer. Each dose contained $10^{6.5-7.5}$ fluorescent focus units (FFU) of live attenuated influenza virus reassortants of each strain. Immunization was administered in two 0.1 mL volumes (separated on the sprayer by a dose divider clip) in each nostril. The study was conducted over two consecutive influenza seasons and thus utilized different vaccine formulations. In 2012-2013, the seasonal influenza vaccine was trivalent and contained A/California/7/2009 (H1N1-like), A/Victoria/361/2011 (H3N2-like), and B/Wisconsin/1/2010-like (Yamagata lineage) antigens. In 2013-2014, the seasonal influenza vaccine was exclusively quadrivalent and contained A/California/7/2009 (H1N1-like), A/Victoria/361/2011 (H3N2-like), B/Massachusetts/2/2012-like virus (B/Yamagata lineage), and a B/Brisbane/60/2008-like virus (B/Victoria lineage).

Sera for testing of anti-hemagglutinin antibody was collected at baseline, and at 28 (± 7) days post-vaccination. Influenza-specific antibodies were quantified by hemagglutination-inhibition (HAI) assays using standard procedures [4]. Briefly, sera were treated at a 1:3 ratio (vol/vol) with receptor-destroying enzyme (RDE) at 37°C for 18 to 20h to eliminate non-specific inhibitors of agglutination. RDE were subsequently inactivated by incubation at 56°C for 45-min, followed by addition of 6 volumes of

phosphate-buffered saline (PBS) resulting in an initial testing dilution of 1:10. All RDE-treated sera were tested for non-specific agglutinins, and positive sera were heme-adsorbed using turkey erythrocytes prior to performing HAI assay. HAI assays were performed in V-bottom 96-well microtiter plates and each sample was tested in duplicate.

Influenza virus standardized to 8 hemagglutinin units (HAU) per 50 μ L (4HAU per 25 μ L) in PBS were added to two-fold serial dilutions of test sera. Following incubation at room temperature for 30 min, 0.5% turkey red blood cells containing an abundance of α 2, 6-galactose (α 2,6-Gal)-N-acetyl sialic acid residues were added. Plates were observed for agglutination after 30 min. The HAI titer was defined as the reciprocal of the highest dilution of serum that completely inhibited hemagglutination. The geometric mean titer (GMT) was calculated for each sample duplicate and reported as the final titer. For computational purposes, titers of < 1:10 were assigned a value of 1:5 and those > 1:1280 were assigned a value of 1:1280. Pre- and post-vaccination serum was processed simultaneously.

Responses to vaccination were assessed with measurement of anti-hemagglutinin geometric mean titers (GMT), post-vaccination titer levels and fold-rises from baseline, to each of the three or four influenza reassortants included in the vaccine.

Seroresponse was defined as a post-vaccination hemagglutinin antibody inhibition (HAI) titer $\geq$ 1:40. Seroconversion was defined as a pre-vaccination hemagglutinin antibody

inhibition (HAI) titer $<1:10$ AND a post-vaccination HAI titer $\geq 1:40$ or a pre-vaccination HAI titer $\geq 1:10$ and a minimum four-fold rise in post-vaccination titer.

At the baseline visit, subjects completed a brief questionnaire regarding the preferred method of vaccine administration. In addition, a reactogenicity diary was issued at baseline. Subjects were instructed to complete the diary from study days 0-7, recording the presence and severity of any local or systemic reactogenicity events following vaccination.

Determination of immunologic non-inferiority was based on the following criteria: [1] the upper limit of the two-sided 95% confidence interval (CI) of the GMT ratio (HCWA vaccine / SA vaccine) for any vaccine strain did not exceed 1.5; [2] the upper limit of the two-sided 95% CI for the difference in seroconversion rates (HCWA vaccine – SA vaccine) for any vaccine strain did not exceed 0.10.

Proportions were compared using a χ^2 statistic where $p < 0.05$ was considered statistically significant. When comparing three groups, if at least one was different, pairwise comparisons of proportions were made to identify the different group. No adjustments for multiple comparisons were made. Medians were compared using nonparametric tests for location or scale differences were based on a Wilcoxon or median test. For tests comparing three groups, Kolmogorov-Smirnov tests were used. Analyses were restricted to those participants meeting the per protocol definition.

Written informed consent was obtained at enrollment. The study was approved by the Infectious Disease Institutional Review Board of the Uniformed Services University of the Health Sciences (IDCRP-070).

RESULTS

A total of 1197 individuals were recruited for the trial. Of these, 1077 (90%) were eligible, provided written informed consent and were randomized (Figure 1). By site, enrollment was similar (San Antonio, n=530; San Diego, n=547). The majority (65.5%) of participants were enrolled in the second season. By study group, the distribution was as follows: health care worker-administered (HCWA; n=548), self-administered (SA)/singleton (n=186), SA/groups of 5 (n=174), and SA/groups of 10 (n=169). A total of 1024 were included in the per protocol analysis. The primary reason for exclusion from the final analysis was loss to follow up (n=33; 62%). The proportions of those excluded from analysis did not differ by study group.

The baseline characteristics of the study participants are shown in Table 1. The majority were male (70.9%), white (66.3%), and an active duty military or reserve member (88.3%). The median age was 29 (IQR: 25, 37) years. Those randomized to the HCWA group were slightly older (median: 30 vs. 28 yrs; p=0.004). Nearly seventy percent reported receipt of FluMist[®] vaccine in prior years; the proportion did not differ by study group.

In season 1, participants received trivalent vaccine whereas in season 2, the vaccine was quadrivalent. Pre-vaccination GMTs of anti-HA antibody did not differ by study group (Table 2). Pre-vaccination GMTs were higher for A/H1N1 and A/H3N2 as compared to the B/Yamagata and B/Brisbane strains. Post-vaccination GMTs by vaccine strain and by study group (HCWA vs. SA) were: A/H1N1 (45.8 vs. 48.7, respectively; $p=0.43$), A/H3N2 (45.5 vs. 46.4; $p=0.80$), B/Yamagata (17.2 vs. 17.8; $p=0.55$), and B/Brisbane (16.2 vs. 14.7; $p=0.16$). Proportions of seroresponse to A components were high (~67%), while seroresponses to B components were lower (~25%). The proportions of seroresponders did not differ by administration method.

In concert with low post-vaccination GMTs, the rates of seroconversion were poor: <5% of participants demonstrated a significant rise in antibody titer to any of the vaccine components and there were no significant differences in the rates of seroconversion by study group, although the sample sizes of the stratified analyses were small. In a subgroup analysis of participants whose baseline HAI titers were <10, rates of seroconversion were also low (range: 0-6%) and did not differ by study group (data not shown).

Post-vaccination GMT ratios for each of the antigens are displayed in Figure 2. There were no significant differences in immunogenicity of LAIV by vaccination method, as none of the upper limits of the 95% confidence intervals exceeded 1.5.

Local and systemic reactogenicity events were assessed daily through post-vaccination day 7, and there were no differences between study groups with respect to reported adverse events. The most commonly reported local reactogenicity events were nasal

congestion (42.9%), runny nose (40.4%), and sore throat (21.2%). The most commonly reported systemic reactogenicity events were headache (39.9%), tiredness/weakness (35.4%), and myalgia (20.9%). When the frequency of reactogenicity events were compared with self-administered groups, individuals in the self-administered / singleton groups had higher reported frequencies of runny nose (53% vs. 37% vs. 38%; $p<0.01$) and nasal congestion (49% vs. 44% vs. 34%; $p=0.02$) when compared to the self-administered / groups of 5 and self-administered / groups of 10, respectively.

Participants were surveyed pre- and post-vaccination on the preferred method of vaccine administration (Table 3). At baseline, 61% participants cited “No preference” in the method of vaccine administration, with no differences in responses between HCWA and SA study groups ($p=0.93$). In the post-vaccination survey of those who were randomized to self-administration, the majority (63.7%) cited “Self-Administration” as the preferred method of vaccination. Furthermore, there were no differences when those preferring self-administration of vaccine were stratified by sub-group (SA-singleton: 62%; SA-groups of 5: 63%; SA-groups of 10: 66%; $p=0.87$). Five percent of those randomized to the self-administered group reported difficulty with this method of administration, with “Spraying the first half” (3.4%) and “Removing the (dose divider) clip” (1.4%) cited as the major issues.

DISCUSSION

In the setting of a phase IV, randomized controlled trial conducted at two US military facilities, we have shown that self-administered live attenuated influenza vaccine (LAIV) was not inferior to health care worker-administered LAIV with regards to safety and immunogenicity. The feasibility of self-administration was demonstrated not only for participants receiving individualized (i.e., one-on-one) instructions, but also for groups of participants receiving vaccination instructions from a single health care worker. This finding is of particular relevance for the military, because in certain circumstances of rapid deployment and/or mobilization of large numbers of personnel, mass vaccination strategies may be needed to prevent outbreaks of influenza and to ensure force health protection.

Among US active duty military personnel, annual receipt of influenza vaccine is mandatory. At many military facilities, including the two involved in our study, mass vaccination for influenza is conducted by trained health-care workers in the setting of large-scale immunization fairs, typically held in September/October of each year (i.e., prior to the start of the usual influenza season). While this strategy is designed to vaccinate the maximum number of people during a designated period of time, there is a considerable resource requirement with respect to the number and availability of health care workers who are trained to administer vaccines. In our study, self-administered LAIV was not only safe and immunogenic, it was also the preferred method of administration among those who were randomized to the self-administration group.

To our knowledge, three prior studies have evaluated the self-administration of influenza vaccine [5-7], two of them using LAIV [6, 7]. In a non-randomized, multi-center effectiveness trial involving ~3000 participants (of whom two-thirds selected supervised self-administration), vaccinees were followed for a single influenza season for the occurrence of any febrile illness [6]. The incidence of influenza-like illness did not differ by method of administration, and self-reported rates of reactogenicity symptoms and adverse events were similar between groups. Serum was not obtained from participants; therefore, comparisons of immunogenicity by administration method could not be made. The second study of self-administered LAIV, conducted on a much smaller scale, merely assessed the practicality of mass vaccination and did not collect clinical information to evaluate vaccine effectiveness nor serum specimens to evaluate immune response [7].

Our study had a number of strengths, including the randomized allocation of participants to study groups and high rates of follow-up and survey completion. Moreover, the study was executed on an existing infrastructure (i.e., immunization fairs) to which military personnel and beneficiaries were already familiar.

There were limitations to the study. Subjects were not followed for clinical outcomes during the influenza season. Therefore, we were not able to generate comparative estimates of vaccine effectiveness by method of administration. Second, the rates of seroconversion in both groups were low. This may be due to high rates (>90%) of annual immunization coverage in this population, reflecting a degree of immune

tolerance to vaccine antigens after repeated exposures. Third, we employed HAI assays, rather than microneutralization assays, that are less sensitive measures of immunogenicity of LAIV. Lastly, the serologic correlates of protection induced by LAIV may differ from those induced by inactivated vaccines. It is not currently known whether these differences impact vaccine effectiveness. Two studies suggested that inactivated influenza vaccine may be more effective than live attenuated vaccine among routinely immunized military populations [8, 9]. By contrast, a third study of influenza vaccine effectiveness among US military personnel showed no such differences by vaccine type [10].

In summary, self-administration of LAIV is feasible in individual and small group settings. Consistent with others [6], we found that trial participants preferred self-administration as the method of vaccination. Further studies among military populations are needed to evaluate the feasibility and logistics of vaccine self-administration not in health care facilities, but rather, in field-based settings that are more akin to the conditions and circumstances encountered in military deployment. In such field-based studies, a number of additional factors (e.g. maintenance of a cold chain, larger group size, etc.) should be examined to address whether mass vaccination by self-administration is a viable disease prevention strategy for military populations.

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TABLES AND FIGURES

Figure 1. CONSORT diagram of study participants in a phase IV, open-label, randomized controlled trial evaluating the immunogenicity and acceptance of self-administered live attenuated influenza vaccine

Recruitment

Assessed for eligibility (n=1197)

Enrollment

Eligible/Randomized (n=1077)

Excluded (n=120)

Allocation

Allocated to SA-singleton
and received intervention
(n=186)

Allocated to SA-5 $\pm$ 1
and received intervention
(n=174)

Allocated to SA-10 $\pm$ 2
and received intervention
(n=169)

Allocated to HCWA and
received intervention
(n=548)

Follow-up

Lost to follow-up (n=4);
At least one blood draw
outside window (n=4)

Lost to follow-up (n=8);
Personal reason (n=1)
At least one blood draw
outside window (n=1)
Unknown (n=1)

Lost to follow-up (n=6);
Personal reason (n=1)
At least one blood draw
outside window (n=2)

Lost to follow-up (n=15);
Withdrew medical (AE) (n=1)
At least one blood draw outside
window (n=8)
Unknown (n=1)

Analysis

Analysed (n=178)

Analysed (n=163)

Analysed (n=160)

Analysed (n=523)

Table 1. Comparison of baseline characteristics among trial participants by method of vaccine administration

Characteristic	HCWA n=523		SA n=501		p-value
Age (median, IQR)	30 (26, 38)		28 (24, 36)		0.0044 [‡]
Number of days between pre- and post-vaccination blood draw (median, IQR)	27 (22, 29)		27 (22, 29)		0.91
	n	(%)	n	(%)	
Male	366	(70)	360	(72)	0.51
Race					
White, Only	332	(63)	347	(69)	0.02
Black, Only	88	(17)	55	(11)	
Other/Unknown	103	(20)	99	(20)	
Hispanic	103	(20)	101	(20)	0.85
Service					
Army	183	(35)	175	(35)	0.62
Air Force	74	(14)	61	(12)	
Navy	259	(50)	261	(52)	
Marine	7	(1)	4	(1)	
Duty Status					
Active Duty/Reservist	451	(86)	453	(90)*	0.03
Retired Military	27	(5)	11	(2)	
Dependent	45	(9)	37	(7)	
Smoking Status					
Non-Smoker	401	(77)	391	(78)	0.86
Smoker	65	(12)	57	(11)	
Former Smoker	56	(11)	53	(11)	
Previous receipt of FluMist [®]	361	(69)	330	(66)	0.28
Preferred method of vaccine					

Characteristic	HCWA n=523		SA n=501		p-value
administration prior to randomization					
HCWA	71	(14)	64	(13)	0.93
SA	132	(25)	129	(26)	
No Preference	320	(61)	307	(61)	
Current/Past Disease History					
Allergies	175	(33)	163	(33)	0.75
Gastrointestinal	34	(6)	34	(7)	0.85
Hematological	44	(8)	43	(9)	0.92
Neurological	103	(20)	91	(18)	0.53
Cardiovascular	35	(7)	26	(5)	0.31
Genitourinary	13	(2)	18	(4)	0.30
Hepatic	22	(4)	32	(6)	0.12
Endocrine	15	(3)	10	(2)	0.37
HEENT	102	(19)	87	(17)	0.38
Musculoskeletal	30	(6)	26	(5)	0.70
Respiratory	124	(24)	116	(23)	0.83
Other	99	(19)	90	(18)	0.69
Currently taking medication/vitamins/supplements	279	(53)	246	(49)	0.17

HCWA: health care worker-administered; SA: self-administered; IQR: interquartile range; ‡ Wilcoxon test

Table 2. Immunogenicity of seasonal influenza vaccine strains by administration method

	HCWA n=523	SA n=501	
			Proportion (Risk) Difference*
A/H1N1			
GMT, pre-vaccination (95% CI)	44.4 (39.8, 49.5)	52.9 (47.3, 59.3)	
GMT, post-vaccination (95% CI)	45.8 (41.1, 51.1)	48.7 (43.6, 54.5)	
Seroresponse, n (%)	340 (65)	344 (69)	-0.0365 (-0.0941, 0.0211)
Seroconversion, n (%)	15 (3)	5 (1)	0.0187 (-0.0054, 0.0428)
A/H3N2			
GMT, pre-vaccination (95% CI)	42.0 (37.6, 46.8)	45.2 (40.4, 50.5)	
GMT, post-vaccination (95% CI)	45.5 (40.8, 50.6)	46.4 (41.6, 51.8)	
Seroresponse, n (%)	335 (64)	336 (67)	-0.0301 (-0.0882, 0.0280)
Seroconversion, n (%)	8 (2)	7 (1)	0.0013 (-0.0207, 0.0234)
B/Yamagata			
GMT, pre-vaccination (95% CI)	17.3 (16.1, 18.6)	17.6 (16.3, 19.0)	
GMT, post-vaccination (95% CI)	17.2 (15.9, 18.6)	17.8 (16.5, 19.2)	
Seroresponse, n (%)	141 (27)	137 (27)	-0.0039 (-0.0584, 0.0507)
Seroconversion, n (%)	2 (<1)	3 (<1)	-0.0022 (-0.0220, 0.0177)

B/Brisbane (2013-2014 only)	n=346	n=359	
GMT, pre-vaccination (95% CI)	13.8 (12.7, 15.1)	14.9 (13.5, 16.4)	
GMT, post-vaccination (95% CI)	16.2 (14.7, 17.9)	14.7 (13.3, 16.2)	
Seroresponse, n (%)	84 (24)	79 (22)	0.0227 (-0.0396, 0.0850)
Seroconversion, n (%)	23 (7)	14 (4)	0.0275 (-0.0089, 0.0638)

*Non-inferiority analysis, Farrington-Manning Method based on margin of 0.05; HCWA: health care worker-administered; SA: self-administered; GMT: geometric mean titer

Figure 2. Immunologic non-inferiority of health care worker-administered versus self-administered live attenuated influenza vaccine

Table 3. Feasibility of self-administration of live attenuated influenza vaccine

	HCWA n=523	Self-administered				
		Total n=501	SA: Singleton n=178	SA: 5 +/- 1 n=163	SA: 10 +/-2 n=160	
Prior to Vaccine Administration/Randomization						
Previous receipt of FluMist®	361 (69)	330 (66)				0.28
Preferred method of vaccine administration						
HCWA	71 (14)	64 (13)				0.93
SA	132 (25)	129 (26)				
No Preference	320 (61)	307 (61)				
Following Vaccine Administration/Randomization						
Among those randomized to self-administered group, preferred method of vaccine administration						
HCWA			11 (6)	11 (7)	7 (4)	0.87
SA			111 (62)	102 (63)	106 (66)	
No Preference			56 (31)	50 (31)	47 (29)	
Received adequate instructions for self- administration			178 (100)	163 (100)	160 (100)	-
Had difficulty administering vaccine			11 (6)	10 (6)	4 (2)	0.21
Issues cited among those who had difficulty administering vaccine:			0 (0)	0 (0)	1 (25)	0.16*

	HCWA n=523	Self-administered				
		Total n=501	SA: Singleton n=178	SA: 5 +/- 1 n=163	SA: 10 +/-2 n=160	
Removing rubber tip			0 (0)	0 (0)	0 (0)	---
Inserting sprayer			8 (72)	7 (70)	2 (50)	0.72
Spraying 1 st half			4 (36)	2 (20)	1 (25)	0.84
Removing clip			0 (0)	2 (20)	0 (0)	0.45
Spraying 2 nd half			0 (0)	0 (0)	9 (0)	--
Did not understand						

All p-values in this section are based on Fisher's Exact Test; HCWA: health care worker-administered; SA: self-administered