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Safety, tolerability, and immunogenicity of inactivated trivalent seasonal influenza vaccine administered with a needle-free disposable-syringe jet injector

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ABSTRACT

Background: Jet injectors (JIs) avoid safety drawbacks of needle–syringe (N–S) while generating similar immune responses. A new generation of disposable-syringe jet injectors (DSJIs) overcomes the cross-contamination risk of multi-use-nozzle devices used in 20th-century campaigns. In the first study in humans, the newly-US-licensed LectraJet® model M3 RA DSJI was compared to N–S.
Methods: Sixty healthy adults received one 0.5 mL intramuscular dose of the 2009–2010 seasonal, trivalent, inactivated influenza vaccine (TIV) in randomized, double-masked fashion by either DSJI ($n = 30$) or N–S ($n = 30$). Adverse reactions were monitored for 90 days after injection, and serologic responses assayed by hemagglutination inhibition (HI) at days 28 and 90.
Results: There were no *related* serious adverse events (SAEs), nor differing rates of unsolicited AEs between DSJI and N–S. Solicited erythema and induration occurred more often after DSJI, but were transient and well-tolerated; a trend was noted for fewer systemic reactions by DSJI. Pre-vaccination HI geometric mean titers (GMT) increased by 28 days for H1N1, H3N2, and B antigens by 13-, 14-, and 8-fold via DSJI, and by 7-, 10-, and 7-fold for N–S, respectively. No trending differences in GMT, seroconversion, or seroprotection were noted; sample sizes precluded non-inferiority assessment.
Conclusions: DSJI delivery of TIV is well-tolerated and immunogenic.

1. Background

Needle-free vaccine delivery has the potential to lead to significant advances in immunization, including improved safety for the vaccinator and vaccinee, better compliance with immunization schedules, decreased fear of injection and needles, easier and speedier vaccine delivery, and reduced cost [1]. For these reasons, needle-free vaccine delivery has been supported by the World Health Organization [2], the Global Alliance for Vaccines and Immunization [3], and the Centers for Disease Control and Prevention [4].

Needle-free jet injectors (JI) are devices that use pressure to deliver the drug or vaccine into different parts of the human body, such as skin, muscle, or fat. They have been used since the late 1940s to deliver millions of vaccine doses [5]; the first devices were multiple-use nozzle jet injectors "MUNJIs" whereby the vaccine was delivered through the same fluid stream and nozzle for multiple patients. After an outbreak of hepatitis B virus infection in a weight reduction clinic in 1985 [6], and upon a growing body of evidence for possible cross-contamination, such devices are no longer used in public health [7]. More recent development efforts have resulted in disposable syringe jet injectors, "DSJI", which provide a completely non-reusable fluid pathway so that splash back of blood cannot occur [7].

We report a first human safety and immunogenicity study of trivalent inactivated influenza vaccine (TIV) administered by the LectraJet® M3 RA DSJI, cleared for sale and use by the U.S. Food and Drug Administration in 2009 (FDA 510(k) #K090959) based on substantial equivalence to legally marketed predicate devices [8].

Abbreviations: AE, adverse event; CBC, complete blood count; CDC, centers for Disease Control and Prevention; CHMP, Committee for Human Medicinal Products; CI, confidence interval; DSJI, disposable-syringe jet injection/injector; EMEA, European Medicines Agency; FDA, U.S. Food and Drug Administration; FE, Fisher's exact; GAVI, Global Alliance for Vaccines and Immunization; GMT, geometric mean titers; HBV, hepatitis B virus; HCV, hepatitis C virus; IM, intramuscular; HIV, human immunodeficiency virus; HI, hemagglutination inhibition; JI, jet injector/injection; mm, millimeter; MUNJI, multi-use-nozzle jet injector; NA, not applicable; N–S, needle–syringe; PATH, Program for Appropriate Technology in Health; SAE, serious adverse event; TIV, trivalent (inactivated) influenza vaccine; URI, upper respiratory infection; USAID, United States Agency for International Development; WHO, World Health Organization.

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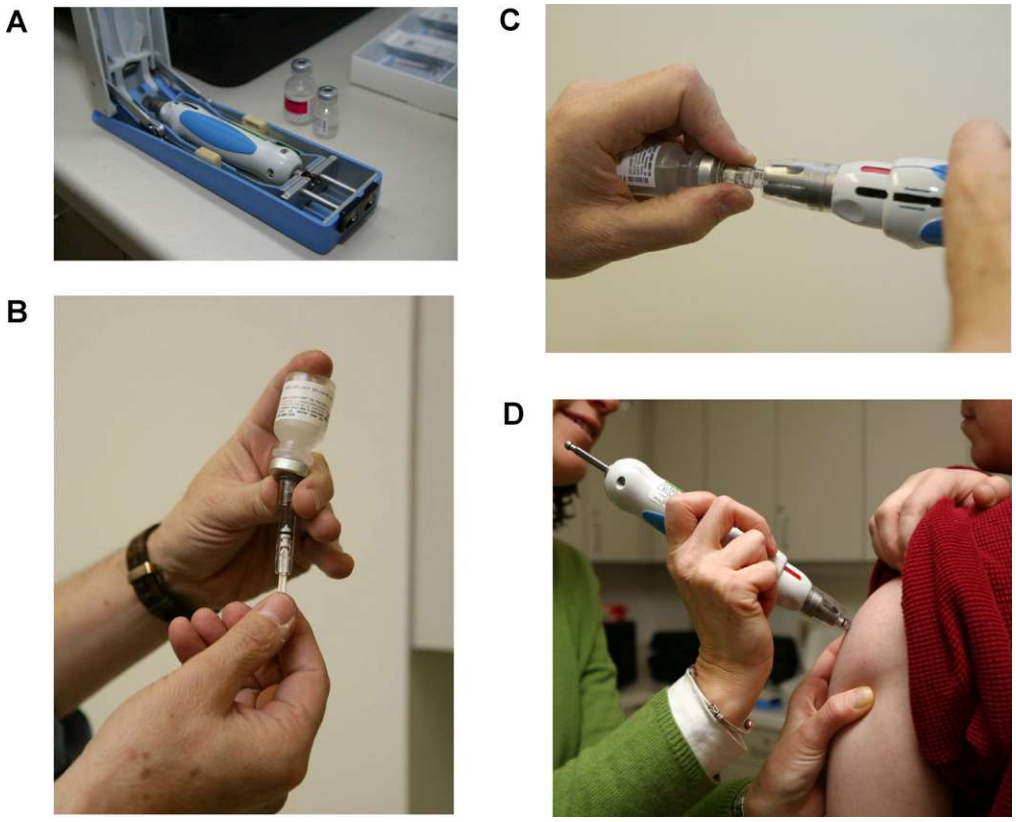

Fig. 1. (A) The LectraJet® M3 RA in its combination storage case and reset station. Upon closing in reset mode, the metal spring of the device is compressed to power the next injection. (B) Manual filling of the LectraJet syringe using a sterile vial adaptor. (C) Engagement of the filled syringe to the injector, before removal of the vial and vial adaptor, which can also be separated beforehand. (D) The injection is activated when the device reaches a pre-set pressure upon application against the limb.

2. Methods

2.1. Subjects

Healthy male and female volunteers aged 18–49 years were recruited from the Baltimore/Washington, DC area for this randomized, controlled, double-masked clinical trial. Volunteers were required to be in good health as evidenced by medical history and physical examination, if indicated. Ineligible were those who received an influenza vaccine in the 2008–2009 or 2009–2010 influenza seasons, received a live-attenuated vaccine within 30 days prior to enrollment or a killed vaccine within 14 days prior to enrollment, were dependent on alcohol or illicit drugs, or were females of childbearing potential with a positive pregnancy test. There were no restrictions on race, ethnic origin, religion, or any social or economic qualifications. Volunteers who satisfied eligibility criteria were randomly allocated into two groups of 30 each to receive licensed, seasonal TIV, either by conventional N–S or DSJI. Investigational Review Board approval, ClinicalTrials.gov registration (identifier NCT00987350), and informed consent of subjects were obtained prior to initiation of enrollment. Good Clinical Practice was utilized throughout the trial.

2.2. Vaccine

All subjects received one 0.5 mL dose from a single lot (U 239 AA) of U.S.-licensed TIV (Fluzone®, Sanofi Pasteur Inc., Swiftwater, PA, USA). The vaccine was non-adjuvanted, formulated as a liquid, and packaged in latex-free 5 mL multi-dose vials containing 10 doses each. It was labeled for the 2009–2010 (Northern Hemisphere) season, and contained 15 μg each of an A/Brisbane/59/2007 (H1N1)-like virus, an A/Brisbane/10/2007 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus. The vaccine was stored refrigerated as per manufacturer's instructions with cold-chain maintained and documented throughout the protocol.

2.3. Double masking

Vaccine was injected into the deltoid muscle either by DSJI or N–S. To prevent volunteers from using sound, sight, or feel to identify their study group, during vaccination, the vaccinees: (1) wore ear earphones playing music loud enough to mask the sound of a jet injector, (2) inserted their non-dominant arm through a medical screen that blocked their vision of the injection event and (3) had the needle inserted through the center of a plastic hollow ring held against the skin for those receiving vaccine by N–S. The ring's diameter was equal to the nozzle of the jet injector syringe, in order to mimic contact by the DSJI syringe. Randomization was performed by an unmasked statistician who provided the allocation code to an unmasked vaccinator not involved in subsequent clinical or immunologic assessments.

2.4. Delivery

Vaccinations by the LectraJet® DSJI (Fig. 1) were performed in accordance with its *Instructions for Use* provided by its manufacturer (D'Antonio Consultants International, Inc., East Syracuse, NY, USA). To use the LectraJet®, the vaccinator manually operates a separate "reset" station which provides mechanical advantage to compress the injector's metal spring (Fig. 1A). Vaccine is loaded into the syringe by attaching it via an adaptor to the vaccine vial, pulling back on its plunger to fill its chamber, then breaking off the distal end of the plunger (Fig. 1B). The filled syringe is then inserted into the injector until its grasping jaws lock onto the flanges of the

Table 1
Demographic characteristics of volunteers assigned to TIV injection by needle and syringe (N–S) and disposable-syringe jet injector (DSJI) administration.

	DSJI (n^a = 30)	NS (n = 30)	Total (n = 60)
Age, mean in years (95% CI[b])	20.6 (19.7–21.4)	20.4 (19.3–21.6)	20.5 (19.8–21.2)
Female, % (95% CI)	43 (25–62)	50 (31–69)	47 (34–60)
Black, % (95% CI)	10 (0–21)	20 (5–35)	15 (6–24)
Asian, % (95% CI)	30 (13–47)	27 (10–23)	28 (17–40)
White, % (95% CI)	60 (42–78)	53 (35–72)	57 (44–70)

[a] Number of volunteers.
[b] Confidence interval.

syringe (Fig. 1C). The injector is then held against the deltoid muscle (Fig. 1D). Upon actuation to release the spring, a rod rapidly pushes the syringe piston/plunger forward, pressurizing and ejecting vaccine through the syringe orifice (diameter: 0.01 in. [0.254 mm]), effecting the injection. The vaccine is delivered to intramuscular tissue as based on performance criteria including injection force and duration as well as depth and dispersion in homogenous substrate (data not shown).

Those in the N–S group were injected intramuscularly using a 25 gauge, 1 in.-long [25.4 mm] needle on a conventional disposable syringe.

2.5. Clinical assessment

Volunteers were observed in the clinic for at least 15 min after inoculation, and their injection sites were photographed. Vital signs including oral temperature (in degrees Fahrenheit) were recorded. The largest diameter of any erythema, induration, and bruising were measured in millimeters (mm) and graded (mild = 1–29 mm, moderate = 30–119 mm, severe ≥ 120 mm). Local symptoms including pain and tenderness were recorded, as were systemic symptoms such as headache, myalgia, and fatigue. Symptoms were graded as mild (does not interfere with activities), moderate (somewhat interferes with activities), and severe (markedly interferes with or prevents activities for ≥24 h). Volunteers were trained to measure and report signs and symptoms. Fifteen minutes after vaccination, volunteers were asked whether they would rate the experience of getting this vaccine as "poor", "acceptable", or "excellent".

Instructions were provided to volunteers to maintain a memory aid to record both prompted and unsolicited local and systemic adverse events (AEs) for 3 days after immunization and to return to the clinic on days 1 (window 1–2 days), 3 (window 3–6), and 7 (window 7–10) after vaccination. Loss of appetite (anorexia) was graded separately as mild (eating typical amount), moderate (eating less than typical amount), and severe (unable to eat for ≥24 h).

Upon return on days 1–2, 3–6, and 7–10 after vaccination, the injection site was again photographed, the memory aid was reviewed by investigators, and a targeted physical examination performed, if indicated. Volunteers returned on days 28 (window 26–36) and 90 (window 80–100) to obtain serum and record intervening unsolicited AEs.

2.6. Measurement of antibody responses

Seed viruses matching the vaccine strains [A/Brisbane/59/2007 (H1N1), A/Brisbane/10/2007 (H3N2) and B/Brisbane/60/2008] and reference antisera were kindly provided by Dr. Alexander Klimov, CDC. Virus stocks were produced in embryonated chicken eggs, as previously described [9]. Hemagglutination inhibition (HI) antibody levels to the three vaccine components were measured by incubating serially diluted serum samples (starting at 1:8) with 4 hemagglutination units of each antigen and turkey erythrocytes, following standard techniques [10]. Positive reference antisera [Influenza A(H1N1) FR-42; Influenza A(H3N2) FR-44; Influenza B FR-48] and negative controls were included in the assays. Sera were pre-treated with receptor-destroying enzyme (Denka Seiken Co., Tokyo, Japan) to inactivate nonspecific inhibitors of viral hemagglutination. HI titers were calculated as the inverse of the highest dilution that inhibited hemagglutination. Seroconversion was defined as achieving a fourfold or greater rise in HI titer with a post-vaccination titer ≥40 if a pre-vaccination titer was ≤10. Seroprotection was defined as achieving an HI titer ≥40 (dilution ≥1:40)

2.7. Statistical analysis

Clinical data were collected on coded, scannable clinical reporting forms that are subsequently scanned using Teleform™ software (Autonomy, Inc. [Cardiff Software], Vista, CA, USA). Data management and statistical analyses were performed with Office Excel 2007 (Microsoft, Seattle, WA, USA), GraphPad Prism 5.0 (GraphPad Software, Inc., La Jolla, CA, USA), and STATA 9.0 (StataCorp LP, College Station, TX, USA). Point estimates and 95% confidence limits were calculated for the proportion of subjects in the DSJI and N–S groups experiencing any grade of local and systemic AEs within three days after vaccination. Point estimates and 95% confidence limits were calculated for the HI geometric mean titer (GMT) for each influenza antigen. A Fisher's exact (FE) test was used to compare the proportion of subjects in the two study groups with any AE, as well as the proportion achieving seroconversion and seroprotection at each time point. A Student's t test was used to compare the measured continuous variables, as well as natural-log-transformed titers on days 0, 28, and 90 between DSJI and N–S variables that were normally distributed; the Mann–Whitney test was used for variables that were not normally distributed. All hypotheses were evaluated using two-sided tests. Demographic information and adverse event reporting were descriptive. A sample size of 30 volunteers in each group provides 80 power at alpha 0.05 (two-sided) to detect a 48% lower HI seroconversion against H1N1 and H3N2 as well as a 53% lower HI seroconversion against B on day 28 after vaccination.

3. Results

Sixty-five volunteers were recruited and sixty enrolled and vaccinated in February and March of 2010. Four recruits were removed from the study prior to vaccination because of the exclusion criteria of current use of antimicrobials (two recruits), a positive pregnancy test (one), and a history of a bleeding disorder (one). Another eligible volunteer changed her mind prior to being vaccinated. All thirty volunteers randomly assigned to the DSJI study arm received the vaccine by that route; all thirty in the N–S group also received their vaccine by the designated route (Table 1). Written memory aids and serology for all planned time points were obtained for all sixty enrollees.

3.1. Clinical assessment

There were no related serious adverse events (SAEs) throughout the clinical trial. One volunteer had an unrelated SAE, a 2-day hospitalization for acute appendicitis with onset 1-day after vaccination.

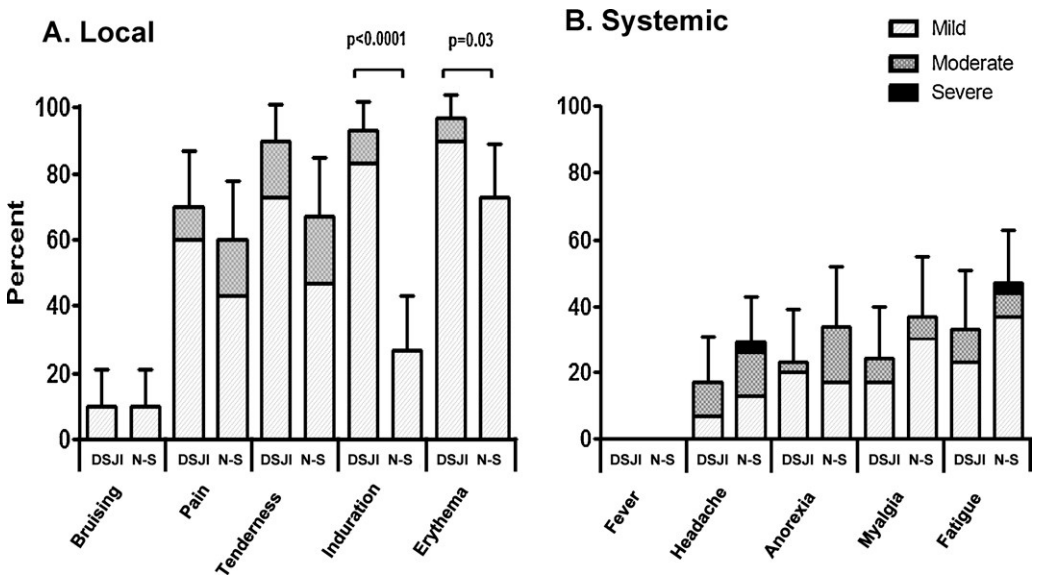

Fig. 2. Comparison of maximal solicited local (A) and systemic (B) reactions during the first three days after vaccination between volunteers receiving licensed 2009–2010 seasonal trivalent inactivated influenza vaccine (TIV) by disposable-syringe jet injection (DSJI) and by needle–syringe (N–S). Error bars indicate the upper 95% confidence interval (CI). The statistically significant *p* values shown derive from two-sided Fisher's exact tests.

A total of 39 unsolicited AEs were reported by 34 volunteers: 25 reported upper respiratory infection (URI), 7 reported unsolicited headache, 3 gastrointestinal upset, 3 musculoskeletal injury, and one urinary tract infection.

Twenty unsolicited AEs were reported by 17 volunteers in the N–S group and 19 unsolicited AEs were reported by 17 volunteers in the DSJI group, without any significant difference between the groups for any unsolicited AE category.

All solicited AEs were mild or moderate, with the exception of severe headache and fatigue on day 2 post-vaccination in a recipient vaccinated by N–S, who had been exposed to contacts with illness, and who developed a URI on day 1 after vaccination.

The most common local AE during the 3 days post-vaccination was erythema, which was seen or reported in 97% of DSJI vaccinees, but in only 73% of the N–S group ($p = 0.03$ by FE). Induration was next in reported frequency, found in 93% of the DSJI group, but in only 27% of the N–S group ($p < 0.0001$ by FE) (Fig. 2A). The mean diameter of the maximum erythema measured in subjects, or among those with any erythema, was 10.4 mm in the DSJI group and 3.5 mm in the N–S group ($p = 0.001$ by Mann–Whitney).

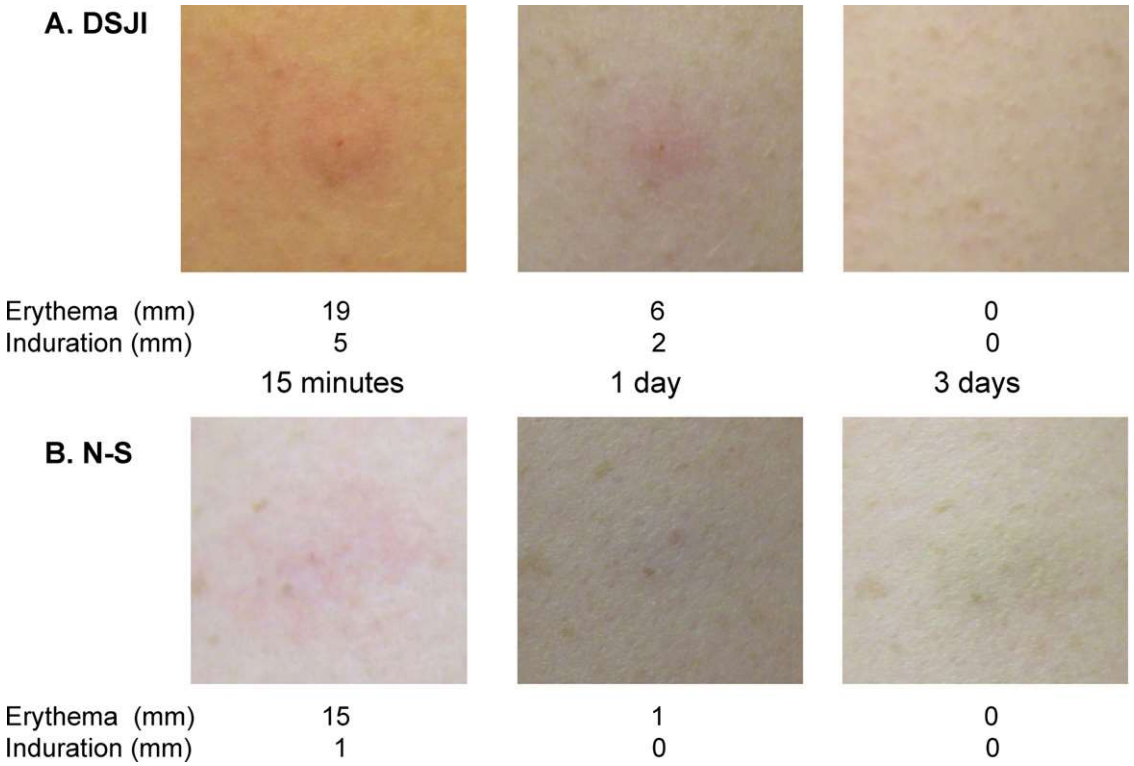

Fig. 3. Serial photographs representing approximately 20 mm × 20 mm sections of skin around injection sites taken of representative volunteers 15 min, one day and three days after receiving vaccine by DSJI (A) and N–S (B). Reported diameters of erythema and induration are reported for the longest axis of measurement, in millimeters (mm).

Table 2
Immunologic responses by hemagglutination–inhibition (HI) assay to antigens of licensed 2010 seasonal trivalent influenza vaccine (TIV), by disposable-syringe jet injector (DSJI) or needle–syringe (N–S) delivery route.

	H1N1			H3N2			B		
	DSJI	N–S	p^a	DSJI	N–S	p^a	DSJI	N–S	p^a
GMT[b] day 0 (95% CI[c])	17 (11–26)	30 (18–50)	0.1	31 (18–52)	30 (16–54)	0.9	14 (9–19)	19 (14–28)	0.1
GMT day 28 (95% CI)	213 (127–357)	199 (131–301)	0.8	426 (253–717)	301 (177–511)	0.3	111 (71–175)	131 (83–206)	0.6
Seroconversion: Percent ≥4-fold rise from day 0 to day 28 (95% CI)	80 (65–95)	63 (45–81)	0.3	80 (65–95)	67 (49–84)	0.4	73 (57–90)	57 (38–75)	0.3
Seroprotection: Percent HI titer ≥40 on day 28 (95% CI)	83 (69–97)	90 (79–100)	0.5	100 (NA)	93 (84–100)	0.5	77 (61–92)	87 (74–99)	0.5

[a] Two-sided independent Student's *t* test on natural log-transformed HI titers for GMT. Two-sided Fisher's exact test for percentages of NS vs. DSJI.
[b] Geometric mean titer.
[c] Confidence interval.

Similarly, the mean diameter of maximum induration was 11.6 mm among DSJI vaccines and 0.8 mm among N–S vaccinees ($p < 0.0001$ by Mann–Whitney). Frequencies of reported local pain, tenderness, and bruising were not significantly different between DSJI and N–S groups, although there was a trend toward slightly higher local pain and tenderness in the DSJI group.

The most common systemic AE was fatigue, reported by 33% of the DSJI group and 47% in the N–S ($p = 0.4$ by FE) (Fig. 2B). Second-most common was myalgia: 23% in DSJI, 37% in N–S ($p = 0.4$ by FE). In contrast to local reaction rates, statistically non-significant trends toward more frequent systemic reactions were reported in the N–S group (Fig. 2B). No volunteers in either group had a temperature greater than 99.6 °F (37.6° C).

All AEs were transient, well-tolerated, and resolved completely. The size of measurable reactions and the severity of graded ones – both local and systemic – peaked on the day of vaccination (day 0) and began improving by day 1 (Fig. 3). No volunteers rated their vaccination experience as "poor". Among the DSJI group, 40% rated it as "acceptable", as did 27% of the N–S group (p = 0.4 FE). An "excellent" experience was described by 60% and 73% of DSJI and N–S groups, respectively ($p = 0.4$ FE).

3.2. Measurement of antibody responses

HI GMT for H1N1, H3N2, and B antigens increased by 13-, 14-, and 8-fold at day 28 post-vaccination for DSJI vaccinees, and by 7-, 10-, and 7-fold for N–S vaccinees, respectively (Table 2). Titers for all antigens decreased by day 90 in both study arms (Fig. 4). The percent of vaccinees that seroconverted by exhibiting a fourfold or greater rise in HI titer from day 0 to 28 among the DSJI group was 80% for H1N1, 80% for H3N2, and 73% for B, and for the N–S group 63% for H1N1, 67% for H3N2, and 57% for B by N–S. The percent of DSJI vaccinees that were seroprotected by achieving an HI titer ≥40 on day 28 were 83% for H1N1, 100% for H3N2, and 77% for B, and for N–S 90%, 93%, and 87%, respectively. There were no statistically significant differences between DSJI and N–S for any of the measured immunogenicity endpoints.

4. Discussion

In this first human clinical study using LectraJet® M3 RA to administer TIV vaccination, injection using the DSJI was found to be well-tolerated and immunogenic. Higher rates of transient local reactogenicity were seen in volunteers vaccinated with the LectraJet device compared to N–S, although a trend toward fewer systemic reactions was also noted.

The traditional administration of vaccines via needles poses safety risks for patients, healthcare providers, and the community [11–13]. An estimated 3 million healthcare workers worldwide are injured annually by N–S and other medical sharps contaminated with hepatitis C virus (HCV), hepatitis B virus (HBV), or human

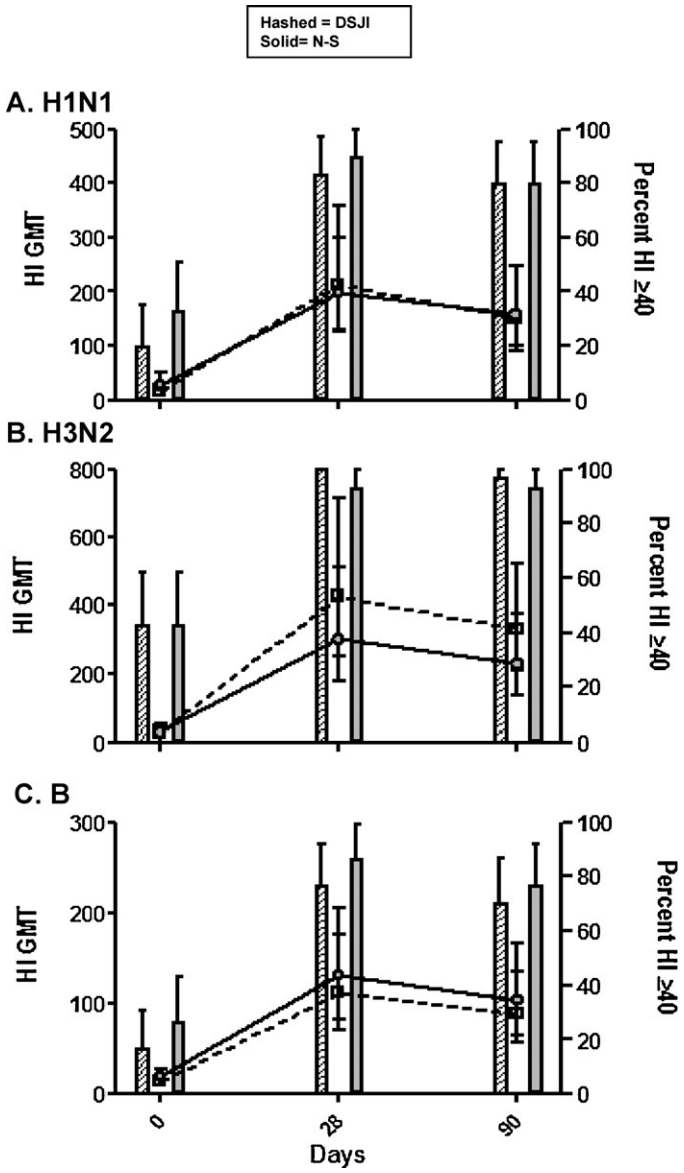

Fig. 4. Geometric mean titers (GMT) (left *y*-axis) of hemagluttination inhibition (HI) assays against H1N1 (A), H3N2 (B), and B (C) vaccine antigens for volunteers vaccinated by DSJI (dashed lines) and by N–S (solid lines). Percentages (right *y*-axis) of DSJI-group (dashed bars) and N–S-group (solid bars) volunteers with HI titers ≥40. The *x*-axis represents the number of days after vaccination. Error bars indicate 95% confidence intervals (CI).

immunodeficiency virus (HIV) resulting in an estimated 16,000 HCV, 66,000 HBV, and 1000 HIV infections [14]. The risk for needlestick injury may substantially increase during the haste of mass vaccination campaigns in response to a bioterrorism emergency or a natural pandemic [15]. Use of DSJIs to administer vaccine obviates the need for needles and thus mitigates this risk and the associated complications. Future high-speed models would allow for delivery of up to 600 vaccinations per hour [8,16], perhaps at reduced overall cost [1,16,17]. The manually powered LectraJet® M3 RA DSJI model used in this study is unique in that it shares its disposable syringes with the still-investigational motorized high speed model.

The medical literature reports that immune responses such as antibody titers and seroconversion rates after vaccination by JI (either MUNJI or DSJI) are sometimes greater than by N–S [7], but the underlying reasons are not known. Theories include wider dispersal of vaccine into immunologically relevant tissues than that achieved by N–S, as well as residual vaccine in the skin and along the track of the jet injector route to its site of primary deposition in fat or muscle [7,16–18]. Such dispersion may enhance contact with antigen presenting cells, lymphocytes, and other effector cells of the immune system. On the other hand, a comparative study of DSJIs vs. N–S for influenza vaccination with sample size groups similar to ours also found no significant differences in immune responses by method of vaccination [19].

Another general finding reported in the JI literature is that this method of vaccination often produces higher rates of local reactions than N–S [7], as borne out in this study, as well. Jackson, et al. found erythema, swelling, and pain more frequent among their two DSJI study arms when compared to the control N–S arm [19]. Another study of JI immunization using the measles, mumps, and rubella vaccine found no difference in pain [20], but its sample size was small and trended toward more pain. These and other studies, including ours, found the increased reactogenicity to be tolerable and not of a severity that would be clinically significant or contraindicate use. Indeed, similar numbers of volunteers in both groups of this study found the vaccination experience “acceptable” or “excellent”.

On the other hand, however, a DSJI study of aluminum-adjuvanted hepatitis B vaccine produced local pain reactions sufficiently obnoxious to cause some volunteers to refuse subsequent doses [21], and another study of adjuvanted hepatitis A virus vaccine found ten times more frequent local reactions among the DSJI group than N–S [18], suggesting that chemical irritability of the product injected may be a major factor in local reactions.

A key limitation to this and similar studies is the small number of participating subjects, which makes difficult any statistically based conclusions on similarities, differences, and non-inferiority between study groups. Instead, our study was intended as a first analysis of the safety and tolerability of a new needle-free system for vaccine delivery, and its ability to satisfy accepted standards for immune response to influenza vaccine.

In 2007, the FDA issued a Guidance for Industry for the clinical data needed to support licensure of seasonal inactivated influenza vaccines [22]. The recommendation is that HI GMT and rates of seroconversion (defined as percentage of subjects with either a pre-vaccination HI titer <10 and post-vaccination titer ≥40 or a pre-vaccination titer ≥10 and a fourfold or greater rise in post-vaccination titer) be used as immunogenicity endpoints [22]. For adults <65 years of age, the lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion should meet or exceed 40%, and the lower bound of the two-sided 95% CI for the percentage of subjects achieving a titer ≥40 should meet or exceed 70%. This study was not powered for such criteria and thus has wide confidence intervals. However, seroconversion and seroprotection were high enough to satisfy the FDA criteria for four of six (4/6) assessments in the DSJI group and five of six (5/6) assessments for the N–S group; the lower bounds of the 95% CI of the FDA cutoff is missed by 1% for H1N1 and 9% for B in the DSJI group and by 2% for B in the N–S group. It is to be noted that satisfying FDA guidance for TIV licensure is not required for licensed medical devices such as the LectraJet® M3 RA, nor the licensure of N–S devices. It is reassuring, however, that the DSJI immunogenicity reported here is similar to that for N–S delivery, and close to satisfying FDA guidelines despite the small size of this study.

In conclusion, needle-free jet injection of TIV by the newly-licensed LectraJet® M3 RA device appears to have an acceptable safety profile and induce satisfactory immune responses. Future studies should be powered to confirm the observed trends for potential differences and non-inferiority with respect to the N–S route.

Acknowledgments

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