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Original Article

A randomized controlled study to assess the immunogenicity and tolerability of a 2012 trivalent seasonal inactivated influenza vaccine administered via a disposable syringe jet injector device versus a traditional pre-filled syringe and needle ☆

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ABSTRACT

The Stratis® disposable syringe jet injection (DSJI) system (PharmaJet Inc., Denver, USA) delivers vaccine utilizing a spring powered energy source to create a fine high-velocity jet of liquid that directly penetrates the skin without using a needle. We performed a study to collect data on the effect of the Stratis DSJI device on influenza immunization in 46 predominantly elderly subjects (28M, 18F; mean age 61 years) who were randomized 1:1 to receive Fluvax 2012 trivalent inactivated influenza vaccine via prefilled N–S or Stratis DSJI. H1N1 seroprotection was not significantly different for vaccine delivered by DSJI (86.4%, 95% CI 72.1–100) or N–S (79.2%, 95% CI 63.0–95.4), and likewise for H3N2 and B strains. The DSJI had a ~2-fold higher mean injection pain score (DSJI: 3.0 versus N–S 1.58, $p = 0.045$) plus increased rates of swelling and tenderness but this was offset by a lower rate of elicited systemic reactions, particularly the frequency of post-immunization headaches (DSJI: 9% vs N–S: 33.3%). This study suggests that subject to confirmation of non-inferiority in an appropriately powered study, the Stratis DSJI is a viable alternative strategy for the administration of seasonal influenza vaccines with particular appeal for individuals with needle phobia. Australia New Zealand Clinical Trials Register: ACTRN12612000709842.

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1. Introduction

Influenza is a highly contagious and potentially deadly viral disease, particularly in the elderly, those with chronic disease and young children. Seasonal trivalent inactivated influenza virus (TIV) vaccines are used to boost neutralizing antibody titers and thereby help prevent severe disease. TIV vaccines are most commonly administered either by intramuscular or deep subcutaneous injection using a needle and syringe (N–S) method. Although this is a reliable and well-tested method, downsides include the risk of needle stick injuries to the operator [1] and avoidance of immunization by subjects suffering from needle phobia [2]. Alternative approaches for TIV vaccine administration include aerosol delivery or mucosal application [3,4], intradermal injection [5], and transdermal patch [6]. In particular, recent advances in intradermal delivery devices, e.g. the Soluvia™ id-needle system (Becton-Dickenson, USA) has enabled intradermal influenza vaccines to be developed for the first time as commercial products, e.g. Intanza® (Sanofi Pasteur, Lyon, France). Another major advance in vaccine delivery has been in the area of jet injector devices [7] including the recently-developed Stratis disposable syringe jet injection (DSJI) device. The Stratis DSJI delivers vaccine using a hand-held, spring-powered, energy source to create an extremely fine high-velocity jet of liquid that directly penetrates through the skin without the need for a needle. The Stratis DSJI is approved as a medical device for human use by the US Food and Drug Administration (FDA) and employs a single-use, sterile, auto-disable needle-free syringe for vaccine delivery. The delivery of TIV vaccine through this needle-free device could offer a superior experience compared to N–S injection, particularly for needle

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phobic subjects, with an added advantage being removal of needle stick injury risk.

Vaccine labeling is clear on the route of parenteral administration (IM, SC, ID), but is most often silent on the method of administration. While N–S is most commonly used, DSJI devices have been used for over 50 years across a wide range of vaccines [7–10]. However, on October 26th, 2011 the US FDA issued a communication to "inform the public that inactivated influenza vaccines labeled for IM injection are intended for administration using a sterile needle and syringe." This recommendation was based, in part, on the fact that safety and effectiveness information submitted to the FDA by vaccine manufacturers in support of the influenza vaccine approvals were acquired with N–S, and not DSJI. This delivery method-specific approach to vaccine approval signals a significant departure on the part of the FDA from previous practice.

The primary aim of this pilot clinical study was to test the utility of the Stratis DSJI for delivery of TIV vaccine as compared to a preloaded N–S with the aim of collecting data to inform the design of a larger, appropriately powered, immunogenicity non-inferiority study. A secondary aim was to collect preliminary data on the frequency and severity of local and systemic side effects between the two administration approaches and to assess subject satisfaction with the Stratis DSJI device.

2. Methods

2.1. Study site

The study was conducted as a single site study sponsored by Vaxine Pty Ltd. and performed within the Australian Respiratory and Sleep Medicine Institute at Flinders Medical Centre (FMC), Adelaide, Australia with recruitment undertaken between March 30, and August 24, 2012. The study was approved by the Flinders Clinical Research Ethics Committee. The study was registered on the publicly accessible Australia New Zealand Clinical Trials Register (http://www.anzctr.org.au) under the trial record number ACTRN12612000709842.

2.2. Study subjects

After obtaining informed consent adult volunteers were randomized to receive their TIV vaccine through either the Stratis DSJI or a preloaded N–S on a 1 to 1 basis. Randomization was performed by use of blinded envelopes containing randomization codes prepared independently using the randomization program available at http://www.radomization.com. The study population included ambulatory subjects and did not exclude those of older age or with chronic disease. Inclusion criteria included males or females 18 years or older, able to provide written informed consent and willing to comply with the protocol for the study duration. Exclusion criteria included history of vaccination with 2012 seasonal influenza vaccine or of serious vaccine or egg allergy, women of childbearing potential unless using a reliable and appropriate contraceptive method, pregnant or lactating women, receipt of another investigational agent within 14 days preceding initiation of treatment or any other serious medical, social or mental condition which, in the opinion of the investigator, would be detrimental to the subjects or the study.

2.3. Study vaccine and devices

Fluvax 2012 (CSL Ltd., Parkville, Australia) was purchased as a single dose preloaded plastic syringe with staked needle containing 15 ug hemagglutinin (HA) dose of each of A/California/7/2009 (H1N1pdm09), A/Perth/16/2009 (H3N2) and B/Brisbane/60/2008 in a volume of 0.5 ml. In the control needle and syringe (N–S) group the vaccine was administered as supplied by the manufacturer in a prefilled syringe with 1/2′ needle for deep subcutaneous/intramuscular injection into the deltoid muscle. For the Stratis DSJI group, immediately prior to use 2 vials of Fluvax 2012 vaccine were dispensed into a sterile 2 ml vial and then using the filling adaptor supplied by PharmaJet, 0.5 ml of the vial contents were aspirated into the DSJI syringe which was then loaded onto the Stratis DSJI device prior to injection into the deltoid muscle. Due to the very different nature of the delivery devices, neither subjects nor clinical staff were blinded to the study arm to which subjects were randomized.

2.4. Study visits

After assessment for eligibility criteria and providing informed consent, study subjects had a baseline clinical assessment, including medical history. Blood samples were drawn for measurement of baseline titers of anti-influenza antibodies. Each eligible subject was then randomized to receive vaccination in one of the study groups. Immediately following immunization subjects recorded their pain score using a visual analogue chart. Subjects were observed for 30 min following immunization and then rescored their pain with the same visual analogue chart. Those subjects who received their vaccine via the Stratis DSJI were asked to complete a copy of a questionnaire to assess their perceptions of the injection. Subjects were then provided with a diary to take home with them to record any symptoms or adverse events. Day 1 post-immunization subjects were telephoned to check their condition and to enquire about any adverse reactions. They then returned on day 28 post-immunization for collection of the subject diary, recording of any additional adverse events, and to provide a final blood sample for immunogenicity studies. Adverse events were graded using the "FDA/CBER toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventative vaccine clinical trials" (www.fda.gov/cber/gdlns/toxvac.htm). Those subjects who received their vaccine via the Stratis DSJI were also asked at this final visit to complete a second copy of the questionnaire they had completed previously. The CONSORT Flow Diagram for the study is shown in Fig. 1.

2.5. Influenza assays

Red blood cell hemagglutination inhibition assays were performed in the Dept. of Endocrinology, Flinders Medical Centre using previously described techniques [11]. They were performed against each of the vaccine strains, namely A/California/7/2009 (H1N1), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008 on serum samples of all subjects taken prior to immunization and at 28 days post-immunization.

2.6. Statistical evaluation

The analysis included listings of objective response according to currently pertaining WHO influenza vaccine criteria using the hemagglutination inhibition (HI) assay, including seroconversion = 4-fold increase in titer over baseline, seroprotection = post-immunization titer of 1:40 or greater and potency = Geometric Mean of Titer (GMT) Ratio. Exact binomial confidence intervals were reported for all proportional end points. Reported p-values are two-sided, with no adjustment for multiple testing; $p \leqslant 0.05$ was considered significant. GMT and 95% confidence intervals were computed by taking the exponent of the mean and of the lower and upper limits of the 95% confidence intervals of the $\log_e$-transformed titers. Differences in mean values were compared

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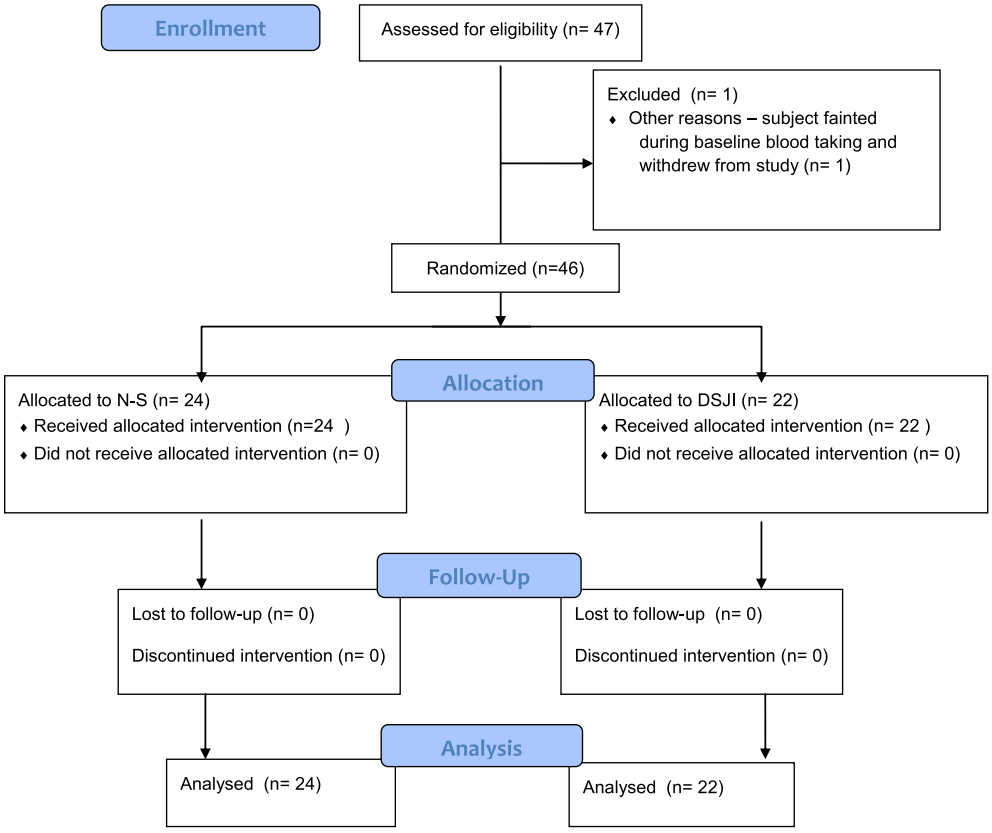

Fig. 1. CONSORT 2010 Flow Diagram –2012 Influenza Vaccine DSJI Study.

with Student *t*-test and for proportions using the Fisher's exact test using the GraphPad online calculator. As this was a pilot study, no formal sample size estimation was performed. A minimum sample size of 20 subjects per group was chosen in order to provide adequate evaluation of the study endpoints and allow estimates of treatment effect to be generated to guide power calculations for design of a future larger non-inferiority study.

3. Results

3.1. Demographics

Twenty-four subjects received Fluvax by staked needle and syringe (N–S group) and 22 subjects received the same Fluvax vaccine via the Stratis DSJI (DSJI group). Overall, the two groups were well matched, although there was a slightly higher mean age and ratio of male to female subjects in the DSJI group (Table 1). This was an older population with mean age over 60 years, and the majority of subjects (>90%) were taking one or more medications for chronic medical conditions. All subjects completed the study protocol with no withdrawals due to post-immunization adverse events and no subjects being lost to follow up.

Table 1
Subject demographics.

	N–S	DSJI
Number of subjects	24	22
Male: *n* (%)	13/24 (54%)	15/22 (68%)
Female: *n* (%)	11/24 (46%)	7/22 (32%)
Age: mean (SD)	59.5 (16.1)	62.5 (9.8)
Age: 18–59 years: *n* (%)	6 (25%)	7 (31.8%)
Age: 60–78 years: *n* (%)	18 (75%)	15 (68.2%)
Caucasian (%)	24/24 (100%)	22/22 (100%)
Previous flu vaccine *n* (%)	23/24 (96%)	22/22 (100%)
On chronic medication *n* (%)	22/24 (92%)	20/22 (91%)

3.2. Vaccine immunogenicity

Vaccine efficacy as measured by hemagglutination inhibition (HI) responses to immunization was modest (Table 2), which likely reflected the elderly demographics of the study population, with such subjects known to have reduced TIV vaccine responses [12]. For the H1N1 vaccine strain, the proportion of subjects achieving a seroprotective titer was not significantly different between the DSJI group (86.4%, 95% CI 72.1–100%) and the N–S group (79.2%,

Table 2
Vaccine efficacy.

	N–S (95% CI)	DSJI (95% CI)
A/California/7/2009 (H1N1)		
GMT (pre/post)	29.1/75.5	34.2/80.0
Seroconversion	33.3% (14.4–52.2)	31.8% (12.3–51.3)
Seroprotection	79.2% (63.0–95.4)	86.4% (72.1–100)
GMT fold increase	2.6 (1.4–3.8)	2.3 (1.3–3.4)
A/Perth/16/2009 (H3N2)		
GMT (pre/post)	23.8/42.4	23.4/49.9
Seroconversion	12.5% (0.7–25.7)	31.8% (12.3–51.3)
Seroprotection	66.7% (47.8–85.6)	72.7% (54.1–91.3)
GMT fold increase	1.8 (1.0–2.6)	2.1 (1.1–3.2)
B/Brisbane/60/2008		
GMT (pre/post)	11.2/16.8	15.5/22.0
Seroconversion	4.1% (3.8–12.0)	4.5% (4.2–13.2)
Seroprotection	16.7% (1.8–31.6)	18.2% (2.1–34.3)
GMT fold increase	1.5 (0.9–2.1)	1.4 (0.7–2.2)

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95% CI 63.0–95.4%, n.s.). A similar result was obtained for the H3N2 and B vaccine strains (Table 2).

3.3. Vaccine tolerability

Post-immunization pain scores were assessed by visual analogue pain charts completed by study subjects immediately following and then 30 min post-immunization. Overall, both injection methods were well tolerated (Fig. 2). The DSJI was associated with a significantly higher mean pain score at the time of injection (mean pain score – DSJI 3.0 versus N–S 1.58, $p = 0.045$ by Student t-test) with several subjects in the DSJI group reporting pain scores of 8 or more out of 10. Overall, the proportion of subjects recording pain scores of 3 or higher at the time of immunization was higher for the DSJI group (10/22, 45.4%; 95% CI 24.6–66.2%) than the N–S group (4/24, 16.6%; 95% CI 1.7–31.5%, $p = 0.05$ by Fisher's exact test). However, in all cases injection site pain abated rapidly and there was no significant difference between groups in injection site pain scores 30 min post-immunization, with no pain score in the DSJI group greater than 3 out of 10 by this time.

3.4. Local adverse reactions

Local injection site reactions were ascertained by a telephone call to all subjects the day following their immunization, and by records from subject diaries returned on post-immunization day 28. Subjects were asked to record in their diary the occurrence of any local reactions (pain, tenderness, redness, swelling and bruising) and also asked to record its duration and severity (Fig. 3). There were a higher total number of local adverse reactions in the DSJI group (total 43 AE amongst 22 subjects) than in the N–S group (total 19 AE amongst 24 subjects). In particular, there were significant differences in rates of tenderness (DSJI: 17/22, 77%; 95% CI 59.41–94.59% versus N–S: 10/24, 41.7%; 95% CI 21.97–61.43%; $p = 0.02$ Fisher's exact test) and swelling (DSJI: 10/22, 45.5%; 95% CI 24.7–66.3% versus N–S: 1/24, 4.2%; 95% CI −3.83–12.23%, $p < 0.001$) with a non-significant trend towards higher rates of bruising and redness in the DSJI group. However, all of the local reactions in the DSJI group were graded as mild only (Grade 1) with just one case of Grade 2 tenderness occurring in the N–S group. Most local reactions abated within 4 days with the majority lasting less than 2 days.

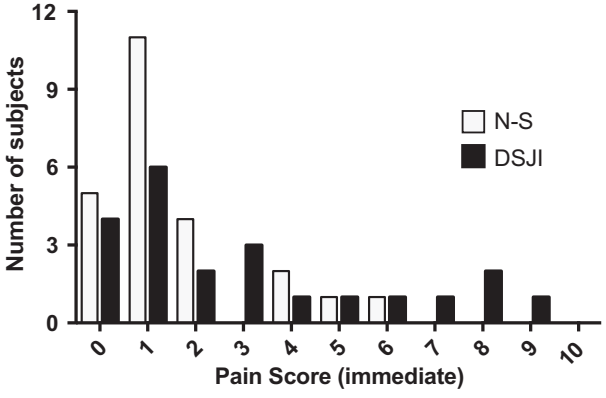

Fig. 2. Post-immunization pain scores of influenza vaccine administered by Stratis DSJI or needle and syringe (N–S). Post-immunization pain scores assessed by visual analogue pain charts recording pain on a scale of 0 (no pain) to 10 (worst imaginable pain) completed by study subjects immediately following influenza immunization.

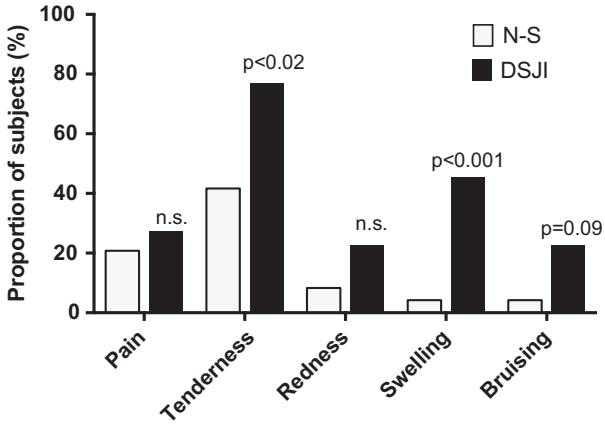

Fig. 3. Local adverse events for influenza vaccine administered by Stratis DSJI or needle and syringe (N–S). Subjects were asked to record any symptoms or adverse events in a diary they took home with them and then returned on day 28 post-immunization.

3.5. Systemic adverse reactions

Systemic adverse reactions were ascertained by a telephone call to all subjects the day following their immunization, and by records from subject diaries returned on day 28. Subjects were asked to record in their diary the occurrence of any systemic reactions (fever/chills, headache, muscle ache, fatigue, nausea, diarrhea) and to record its duration and severity. By comparison to local reactions, which were higher in the DSJI group, there was a significantly lower rate of elicited systemic reactions (fever, headache, muscle ache, fatigue, nausea, diarrhea) in the DSJI compared to the N–S group. Significantly fewer subjects ($p = 0.02$) in the DSJI group (2/22, 9.1%; 95% CI −2.92–21.12%) experienced one or more systemic reactions as compared to the N–S group (10/24, 41.7%; 95% CI 21.97–61.43%). Interestingly, there was a strong trend that did not quite reach statistical significance ($p = 0.07$) to a reduced rate of headaches (Grade 1 or 2) post-immunization in the DSJI group (2/22, 9.1%, 95% CI −2.92–21.12%) compared to the N–S group (8/24, 33.3%, 95% CI 14.44–52.16%).

3.6. Subject perceptions of the stratis DSJI device

A simple questionnaire was administered to all subjects who received immunization via the DSJI, both immediately after immunization and again on the Final Study Visit on day 28 (Table 3). A high frequency of subjects in the DSJI group (77.3%) reported no anxiety or fear about needles. Immediately after immunization 86.4% of subjects reported being moderately to extremely satisfied with having the influenza vaccine through the DSJI and 81.8% still felt this way 4 weeks later. Subject acceptability of the DSJI was high, with over 81.9% expressing a moderate to extreme interest in having their next vaccine using the DSJI. Two subjects (9.1%) reported immediately post-immunization being not at all satisfied with the DSJI which correlated with very high injection pain scores reported by the same subjects (data not shown).

4. Discussion

The study within the limitations of its size and power demonstrated that administration of TIV vaccine via the Stratis DSJI had no adverse effect on TIV immunogenicity when compared to administration via the pre-filled N–S. This is consistent with the findings of a recent comprehensive review by Weniger and Papania of alternative vaccine delivery methods that concluded the

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Table 3
Stratis DSJI consumer questionnaire.

Questions	Answers	Day 0 (n = 22)	Day 28 (n = 22)
Q1. Do you have anxiety or a fear of needles?	Not at all	17 (77.3%)	21 (95%)
	Mildly	3 (13.6%)	1 (4.5%)
	Somewhat	1 (4.5%)	0
	Moderately	1 (4.5%)	0
	Extremely	0	0
Q2. Overall, how painful or physically uncomfortable was your needleless injection?	Not at all	8 (36.4%)	10 (45.5%)
	Mildly	7 (31.8%)	7 (31.8%)
	Somewhat	3 (13.6%)	1 (4.5%)
	Moderately	3 (13.6%)	2 (9.1%)
	Extremely	1 (4.5%)	2 (9.1%)
Q3. How satisfied were you with having your flu vaccine via a needleless injection?	Not at all	2 (9.10%)	0
	Mildly	0	1 (4.5%)
	Somewhat	1 (4.5%)	3 (13.6%)
	Moderately	6 (27.3%)	5 (22.7%)
	Extremely	13 (59.1%)	13 (59.1%)
Q4. If it were available, would you want to have your next vaccine via a needleless injection?	Not at all	2 (9.1%)	2 (9.1%)
	Mildly	0	4 (18.2%)
	Somewhat	2 (9.1%)	0
	Moderately	8 (36.4%)	2 (9.1%)
	Extremely	10 (45.5%)	14 (63.6%)
Q5. How likely are you to recommend needleless injections to a friend or family member?	Not at all	3 (13.6%)	1 (4.5%)
	Mildly	0	4 (18.2%)
	Somewhat	2 (9.1%)	2 (9.1%)
	Moderately	9 (40.9%)	4 (18.2%)
	Extremely	8 (36.4%)	11 (50%)

immunogenicity of jet injectors to be usually equal to, if not better than, vaccine administered by N–S [13]. Notably, no studies of TIV vaccine administered via DSJI devices have found a reduction in vaccine immunogenicity [14,15]. The TIV data obtained with at least four different DSJI devices should help reassure regulatory bodies including the FDA that administration of TIV by DSJI should be regarded as equivalent to N–S approaches, with definitive proof on this point soon to be available from a large randomized non-inferiority study by Pharmajet currently underway.

From a tolerability standpoint, there was a significant increase in mild local injection site reactions when TIV was administered using the Stratis DSJI, in accord with findings of other DSJI studies [13–16]. However, local reactions abated within 4 days of immunization, with the majority lasting less than 2 days. Subjects also reported a higher overall pain score immediately post-immunization with the Stratis DSJI, in several cases reaching levels of more than 8 out of 10 on a visual analogue scale but reassuringly this pain was transient and in almost all cases had returned to baseline by 30 min post injection.

Systemic adverse events are more serious than local reactogenicity events from a regulatory standpoint. Interestingly, there was a significant reduction in systemic adverse events, particularly headaches, reported by subjects who were immunized with the Stratis DSJI. This reduction in systemic adverse events with the Stratis DSJI is currently unexplained but could possibly reflect differences in the rate of systemic release of antigen with the different injection techniques. Interestingly, a similar but non-significant trend towards reduced systemic reactions was also reported in the study of TIV administered by the LectraJet DSJI device [15]. We speculate that more superficial deposition of the influenza vaccine when administering vaccine using DSJI devices may delay the systemic release of the TIV antigen, and thereby reduce the systemic side effects consequent upon a bolus of antigen entering the systemic circulation.

Subject acceptability of the Stratis DSJI was high with over 50% expressing a moderate to high interest in having their next influenza vaccine using the DSJI. This was a highly subjective questionnaire administered to gain subjects' perceptions regarding the use of the Stratis DSJI. The subject population is drawn predominantly from elderly subjects, most of whom reported having had regular seasonal N–S influenza immunizations in the past. Only 25% of subjects reported anxiety or fear about needles. A different questionnaire outcome may have been found if the questionnaire was administered to a group with a higher rate of needle phobia. However, such subjects were unlikely to volunteer for this study, as there was a 50% chance they would be randomized to receive the vaccine by standard injection. In fact, many individuals enquiring about participation in the study because of publicity of the Stratis DSJI withdrew their interest when they found that there was no certainty that they would receive the vaccine through the needle free device (data not shown). Despite the study population not being a needle-phobic population, there was nevertheless good acceptance of the device by the majority of subjects. Immediately after immunization 90% reported being moderately to extremely happy with having the influenza vaccine through the Stratis DSJI and 80% still felt this way when asked the same question 4 weeks later. Just two subjects reported not being at all satisfied with the use of the device immediately after they had received the vaccine, which correlated with their high reported pain scores. However, one of these subjects relaxed this assessment when asked the same question 4 weeks later.

Overall, this study highlighted the utility and advantages of the Stratis DSJI when compared to traditional N–S vaccine delivery. The device performed well, generated good vaccine immunogenicity, was easy to use with minimal training, and was well accepted by the majority of subjects. While being associated with an increased rate of mild injection site reactions this was offset by reduced systemic reactions including headaches. In markets where prefilled syringes are not used or not available, the current field-filled DSJI format where the healthcare worker transfers the vaccine from the primary glass container into the needle-free syringe just prior to delivery, works well. The technology could however provide further benefit from bringing a pre-filled syringe option to the market. Whilst this pilot study was not powered to assess non-inferiority of influenza vaccine immunogenicity when administered by the Stratis DSJI device, an appropriately powered study

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to address this question is currently underway and when completed should provide reassurance of the suitability of the Stratis DSJI device for routine influenza vaccine delivery.

Disclosures

M.R. is an employee of PharmaJet, the company commercializing the Stratis device.

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