Immunogenicity & Tolerance Study of Influenza Vaccine (Afluria), USA

Needle-free jet injection for administration of influenza vaccine: a randomised non-inferiority trial

Summary

Background Administration of vaccines by needle-free technology such as jet injection might offer an alternative to needles and syringes that avoids the issue of needle phobia and the risk of needle-stick injury. We aimed to assess the immunogenicity and safety of trivalent influenza vaccine given by needle-free jet injector compared with needle and syringe.

Methods For this randomised, comparator-controlled trial, we randomly assigned (1:1) healthy adults (aged 18–64 years) who attended one of four employee health clinics in the University of Colorado health system, with stratification by site, to receive one dose of the trivalent inactivated influenza vaccine Afluria given either intramuscularly with a needle-free jet injector (Stratis; PharmaJet, Golden, CO, USA) or with needle and syringe. Randomisation was done with a computer-generated randomisation schedule with a block size of 100. Because of the nature of the study, masking of participants was not possible. Immunogenicity was assessed by measurement of the hemagglutination inhibition antibody titres in serum for the three viral strains included in the vaccine. We included six coprimary endpoints: three strain-specific geometric mean titre ratios and the absolute differences in three strain-specific seroconversion rates. The immune response of the jet injector group was regarded as non-inferior to that of the needle and syringe group if both the upper bound of each of the three 95% CIs for the strain-specific geometric mean titre ratios was 1·5 or less, and the upper bound of the three 95% CIs for the strain-specific seroconversion rate differences was less than 10 percentage points. We used *t* test for group comparison. This study is registered with ClinicalTrials.gov, number NCT01688921.

Findings During the 2012–13 influenza season of the northern hemisphere, we allocated 1250 participants to receive vaccination by needle-free jet injector (n=627) or needle and syringe (n=623). In the intention-to-treat immunogenicity population, all participants with two serum samples were included (575 in the jet injector group and 574 in the needle and syringe group). The immune response to Afluria when given by needle-free jet injector met the criteria for non-inferiority for all six coprimary endpoints. The jet injector group met the geometric mean titre criterion for non-inferiority for the A/H1N1, A/H3N2, and B strains (upper bound of the 95% CI for the geometric mean titre ratios were 1·10 for A/H1N1, 1·17 for A/H3N2, and 1·04 for B strains). The jet injector group met the seroconversion rate criterion for non-inferiority for the A/H1N1, A/H3N2, and B strains (upper bound of the 95% CI of the seroconversion rate differences were 6·0% for A/H1N1, 7·0% for A/H3N2, and 5·7% for B strains). We recorded serious adverse events in three participants, none of which were study related.

Interpretation The immune response to influenza vaccine given with the jet injector device was non-inferior to the immune response to influenza vaccine given with needle and syringe. The device had a clinically acceptable safety profile, but was associated with a higher frequency of local injection site reactions than was the use of needle and syringe. The Stratis needle-free jet injector device could be used as an alternative method of administration of Afluria trivalent influenza vaccine.

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Introduction

the 1860s, the technology came into use in the 1940s, was introduced by the military and used widely in mass immunisation campaigns.[13,14] An outbreak of hepatitis B infection was linked to the use of the multi-use nozzle jet injectors[14–16] leading to the present jet injectors, which use one-use, disposable cartridges.[17,18]

An extensive body of clinical literature (including findings of several studies on trivalent influenza vaccine) has shown that vaccines given by jet injection generate immune responses that are often similar to those induced by conventional needle and syringe administration.[17–21] Presently, no influenza vaccines in the USA are labelled to be given with a jet injector device.[22]

The present study was undertaken in response to a US Food and Drug Administration (FDA) practice directive of October, 2011,[2] and at the request of the Center for Biologics Evaluation and Research (CBER) of the FDA to compare the safety and show the non-inferior immunogenicity of a trivalent inactivated influenza vaccine given by jet injector versus needle and syringe.

Methods

Study design and participants

We did this randomised, comparator-controlled trial during the 2012–13 northern hemisphere influenza season (the first participant was recruited on Oct 15, 2012, and the last on Dec 20, 2012) in individuals who presented to the employee health influenza immunisation clinics of the Medical Center of the Rockies (Loveland, CO, USA; University of Colorado health system). All health-centre employees were required to receive an influenza vaccination. Additionally, we recruited friends and family of employees. Participants were adult volunteers (aged 18–64 years) who had stable health status with no exclusionary medical or neuropsychiatric disorders and were mainly health-care workers. The appendix lists exclusion criteria.

See Online for appendix

The study was approved by the institutional review boards-1–biomedical of Poudre Valley Hospital (CO, USA) health-system and was done in accordance with the principles established by the 18th World Medical Association General Assembly (Helsinki 1964) and subsequent amendments and clarifications used by the General Assemblies; present FDA regulations; Good Clinical Practice; and local ethical and regulatory requirements. All participants provided written informed consent before enrolment in the trial.

Randomisation and masking

Participants were randomly assigned (1:1) to the jet injector group or the needle and syringe group with a computer-generated randomisation schedule created by a statistician who had no involvement in the rest of the trial. The randomisation was stratified by investigational site with a block size of 100. Because of the nature of the study, patients were not masked to the type of injection device.[19] Different study staff gave the vaccine and assessed safety after the injection. The safety assessor was masked to the device used for injection. Staff who did the haemagglutination inhibition antibody titre assays were masked to the device, participant identity, and day of sampling.

Procedures

The jet injector (Stratis; PharmaJet, Golden, CO, USA) was cleared for sale and use by the Center for Devices and Radiologic Health of the FDA in 2011 (FDA 510(k) number K111517), for 0·5 mL intramuscular and subcutaneous injections of liquid vaccines and drugs. The influenza vaccine (Afluria, bioCSL, Parkville, VIC, Australia; lot 08249221A) was formulated to meet the recommendations for the 2012–13 northern hemisphere influenza season and contained 45 μg of haemagglutinin: 15 μg each of A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2), and B/Hubei-Wujiagang/158/2009. The vaccine was supplied without adjuvant in 5 mL multidose vials.[23]

Participants received one intramuscular injection of the trivalent influenza vaccine (0·5 mL) in the lateral deltoid of the non-dominant arm or the arm preferred by the participant. Participants in the jet injector group who had a wet shot (in which liquid remains on the skin after injection, suggesting incomplete delivery of vaccine) were revaccinated with needle and syringe and continued in the study only for safety endpoints.

We collected blood samples before vaccination (day 0) and 28 days after vaccination. Safety assessments comprised immediate complaints (noted within 30 min after vaccination), solicited adverse events (local and systemic) from the evening of day 0 through the evening of day 6 after vaccination as recorded on a 7-day diary card, assessment on day 28, and spontaneously reported adverse events during the study.

Immediate complaints solicited from participants after vaccination included pain, tenderness, itching, redness, swelling, and bruising at the vaccination site. Participants recorded solicited local reactions (pain, tenderness, itching, redness, swelling, and bruising) and solicited systemic adverse events (fever, headache, malaise, myalgia, chills, nausea, and vomiting) on the 7-day diary card. Spontaneously reported adverse events were recorded separately on a 28-day diary card.

We assessed immunogenicity by measurement of serum concentrations of haemagglutination antibodies specific for the three virus strains included in the vaccine. We did haemagglutination inhibition assays with Focus Diagnostics (Cypress, CA, USA) in triplicate with egg-derived antigen. Titres that were undetectable at the starting dilution were reported as less than 10 and were analysed as 5. We derived geometric mean titre ratios for each virus strain. We established three strain-specific seroconversion rates. Seroconversion was defined as achieving a four times increase in titre after immunisation when the baseline titre was 10 or higher or a titre of at immunisation of 40 or higher when the baseline titre was

less than 10. We calculated geometric mean fold rise in haemagglutination inhibition titre by taking the anti-logs of the mean of the log-transformed fold increase in titre after vaccination over titre before vaccination for each of the three virus strains. Seroprotection was defined as a haemagglutination inhibition titre of 40 or higher.

With the exception of fever, all solicited local reactions (immediate complaints and local reactions on days 0–6) and systemic adverse events on days 0–6 were judged as grade 1 if they did not interfere with activity, grade 2 if they interfered with activity, and grade 3 if they prevented activity (severity scale for fever: 100·4°F to <101·1°F [38·0°C to <38·4°C] for grade 1; 101·2°F to <102·0°F [38·4°C to <38·9°C] for grade 2; 102·1°F to <104·0 °F [38·9°C to <40·0°C] for grade 3).

Outcomes

The primary objective was to show that six coprimary immunogenicity endpoints, the three strain-specific geometric mean titre ratios and the absolute differences in three strain-specific seroconversion rates, met the criteria for non-inferiority of jet injector compared with needle and syringe. The non-inferiority analysis was based on the criteria outlined by the FDA for accelerated approval for licensure of seasonal influenza vaccines[24]. The secondary outcome was to compare the safety profiles of the vaccine given by needle-free jet injector or needle and syringe based on specifically solicited local and systemic reactions through 7 days after vaccination and adverse events spontaneously reported through day 28 after vaccination.

Statistical analysis

We did statistical calculations with SAS (version 9.2.2). To confirm power calculations, we used PASS (version 8.0.15). We analysed safety in all participants who received the vaccination and for whom any follow-up safety data were available for specific safety analyses. We used Fisher's exact test to compare the proportions of participants with adverse events between the two treatment groups. The analysis of severity grade was done for all grades combined and for severe (grade 3) complaints. We did all tests with a two-sided significance level of 0·05, without adjustment for multiple comparisons.

We analysed immunogenicity in two populations: the immunogenicity population, which included all participants who completed the study with no major protocol deviations judged likely to interfere with immune response to the study vaccine, and the intent-to-treat

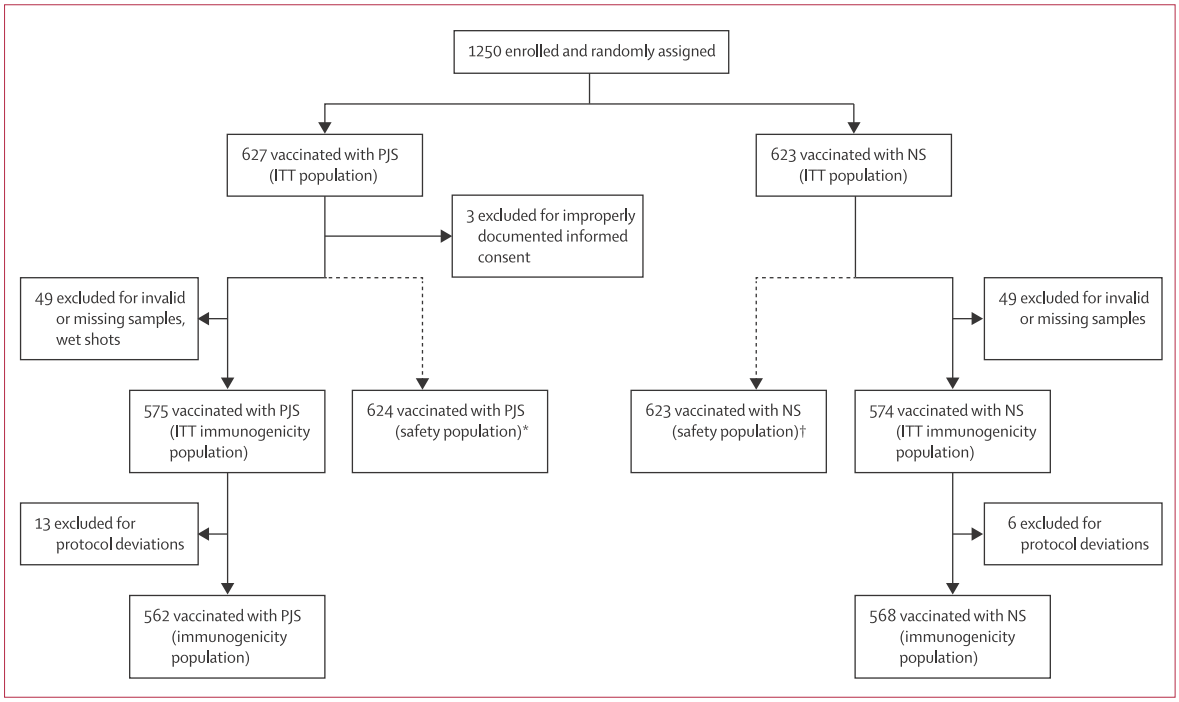

Figure 1: **Trial profile**

The safety population included individuals who received the vaccination and for whom any follow-up safety data were available for a specific safety analysis. The ITT population included all study participants; however, only those with two serum samples could be analysed for immunogenicity (ITT immunogenicity population). The immunogenicity population included all participants who completed the study with no major protocol deviations judged likely to interfere with immune responses in the study vaccine. Reasons for exclusion: 49 participants in the NS group and 43 in the PJS groups were excluded from the ITT population for invalid or missing samples; an additional six who received wet shots in the PJS group were excluded from immunogenicity analysis but were included in the safety analysis. 13 participants in the PJS group and six in the NS group were excluded from the immunogenicity population for the following protocol deviations: second sample collected outside of 28±3 days (PJS n=9 and NS n=4); two sample failures (PJS n=1 and NS n=1); receipt of an additional vaccine (PJS n=2 and NS n=1); failure to meet an inclusion criterion (PJS n=1 and NS n=0). PJS=Pharmajet Stratis needle-free jet injector. NS=needle and syringe. ITT=intention to treat. *n=616 for solicited adverse events days 0–6 because of missing 7-day diary card. †n=607 for solicited adverse events days 0–6 because of missing 7-day diary card.

	ITT and safety population			Immunogenicity population		
	PJS group (n=624)	NS group (n=623)	Total (n=1247)	PJS group (n=562)	NS group (n=568)	Total (n=1130)
Age (years)						
Mean (SD)	41·3 (12·92)	41·5 (12·49)	41·4 (12·70)	41·6 (12·77)	41·8 (12·53)	41·7 (12·64)
Median	41·0	42·0	41·0	42·0	42·0	42·0
Range	18–64	18–64	18–64	18–64	18–64	18–64
Sex						
Men	175 (28·0%)	191 (30·7%)	366 (29·4%)	152 (27·0%)	173 (30·5%)	325 (28·8%)
Women	449 (72·0%)	432 (69·3%)	881 (70·6%)	410 (73·0%)	395 (69·5%)	805 (71·2%)
Race or ethnic origin						
White	595 (95·4%)	600 (96·3%)	1195 (95·8%)	537 (95·6%)	546 (96·1%)	1083 (95·8%)
Not Hispanic or Latino	547 (87·7%)	529 (84·9%)	1076 (86·3%)	495 (88·1%)	480 (84·5%)	975 (86·3%)
Hispanic or Latino	40 (6·4%)	60 (9·6%)	100 (8·0%)	34 (6·0%)	55 (9·7%)	89 (7·9%)
Asian	11 (1·8%)	9 (1·4%)	20 (1·6%)	8 (1·4%)	9 (1·6%)	17 (1·5%)
Black or African American	4 (0·6%)	4 (0·6%)	8 (0·6%)	4 (0·7%)	3 (0·5%)	7 (0·6%)
American Indian or Alaskan Native	3 (0·5%)	1 (0·2%)	4 (0·3%)	2 (0·4%)	1 (0·2%)	3 (0·3%)
Native Hawaiian or other Pacific Islander	2 (0·3%)	0 (0·0%)	2 (0·2%)	2 (0·4%)	0 (0·0%)	2 (0·2%)
Other	9 (1·4%)	9 (1·4%)	18 (1·4%)	9 (1·6%)	9 (1·6%)	18 (1·6%)
Body-mass index						
<25 kg/m² (underweight and normal)	278 (44·6%)	278 (44·6%)	556 (44·6%)	244 (43·4%)	256 (45·1%)	500 (44·2%)
≥25 kg/m² (overweight and obese)	344 (55·1%)	345 (55·4%)	689 (55·3%)	316 (56·2%)	312 (54·9%)	628 (55·6%)
Missing	2 (0·3%)	0 (0·0%)	2 (0·2%)	2 (0·4%)	0 (0·0%)	2 (0·2%)

Data are mean (%) unless otherwise stated. ITT=intention to treat. PJS=PharmaJet Stratis needle-free jet injector. NS=needle and syringe.

Table 1: **Baseline characteristics**

immunogenicity population, which included all participants for whom two serum samples were available, irrespective of protocol deviations. The second blood draw to assess immune response was taken day 28 plus or minus 3 days after vaccination.

The study success was based on achievement of six co-primary endpoints without multiplicity adjustment.[25] Geometric mean titres were summarised by study population, by treatment group, and by visit. Two-sided 95% CIs for the ratios of strain-specific geometric mean titres after vaccination were based on the log normal distribution. We used the natural log values to construct a CI using t-distribution for the mean difference between the two groups. We exponentiated the mean difference and the corresponding CI limits to obtain the geometric mean titre ratio and the corresponding CI. We used the same statistical method to construct CIs for the geometric mean fold rise ratios (needle and syringe/needle-free jet injector).

We summarised seroconversion rates for treatment groups. To show non-inferiority, we established the upper bound of the 95% CI for the proportion seroconversion rate differences with the Newcombe–Wilson score method.[26] We used the same statistical method to construct the CIs for the seroprotection rates.

Immune response of the jet injector group was regarded as non-inferior to that of the needle and syringe group if both the upper bound of each of the three 95% CIs for strain-specific geometric mean titre ratios after vaccination was 1·5 or less, and the upper bound of the three 95% CIs for strain-specific seroconversion rate differences after vaccination was less than 10 percentage points.

Co-This study is registered with ClinicalTrials.gov, number NCT01688921.

Roles of the funding sources

BARDA and PATH are supportive of publication as a means to further their objectives to serve public health but otherwise had no direct involvement in the study or publication. PharmaJet served as the sponsor and took main responsibility for design and execution of the study; bioCSL collaborated closely on the protocol development, study implementation, results analysis, and development of the manuscript. LM, JA, IC, and DKC had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Between Oct 15, 2012, and Dec 20, 2012, 1250 participants were enrolled and were randomised to receive vaccination by jet injector (n=627) or needle and syringe (n=623; figure 1). Three participants were excluded from the jet injector group because of improperly documented informed consent. In the intention-to-treat immunogenicity population, we included all participants with

two serum samples (575 in the jet injector group and 574 in the needle and syringe group). Six participants in the jet injector group received wet shots and were excluded from analysis of immune response but were included in the jet injector safety analysis. The immunogenicity population comprised 562 participants in the jet injector group and 568 participants in the needle and syringe group.

Table 1 shows the baseline characteristics of the two groups. In the intention-to-treat population, median age was 41 years for the jet injector group and 42 years for the needle and syringe group (range 18–64 years); participants were mainly women (72% in the jet injector group and 69% in the needle and syringe group); and were mainly white, non-Hispanic (88% in the jet injector group and 85% in the needle and syringe group).

After one vaccination, both types of administration elicited a similar immune response to the three influenza virus strains contained in the study vaccine (immunogenicity population; figure 2). The geometric mean titre ratio for each influenza strain was about 1. The jet injector group met the geometric mean titre criterion for non-inferiority because the upper bound of the 95% CI of each ratio for the A/H1N1, A/H3N2, and B strains was less than 1·5 (1·12 for A/H1N1, 1·21 for A/H3N2, and 1·06 for B strains). The geometric mean titre ratios in the intention-to-treat immunogenicity population also met the criterion for non-inferiority (upper bound of the 95% CI 1·10 for A/H1N1, 1·17 for A/H3N2, and 1·04 for B strains). The baseline geometric mean titre for both A strains was high in both study groups (figure 2).

The overall rate of seroconversion with jet injector was similar to that with needle and syringe for all three vaccine strains (immunogenicity population; figure 3). In both groups, seroconversion was highest for the A/H3N2 strain and lowest for the B strain (figure 3). The non-inferiority criterion for the difference in seroconversion rate between jet injector and needle and syringe was met for all three strains. The upper bound of the 95% CI on the difference in seroconversion rates for A/H1N1, A/H3N2, and B strains did not exceed 10 percentage points (6·5% for A/H1N1, 7·1% for A/H3N2, and 5·9% for B strains). The seroconversion rate differences were very similar in the intention-to-treat immunogenicity population and met the criterion for non-inferiority (upper bound of the 95% CI 6·0% for A/H1N1, 7·0% for A/H3N2, and 5·7% for B strains)

The geometric mean fold rise in haemagglutination inhibition titres (before and after vaccination) was similar between the two groups. Additionally, the proportion of participants with seroprotection was similar between the two groups. Nearly 100% of the participants in the immunogenicity population achieved a haemagglutination inhibition titre of 40 after vaccination for the two A strains in both treatment groups (data not shown for intention-to-treat population). A haemagglutination inhibition titre of 40 after vaccination for the B strain was achieved by 63·7% in the jet injector group and 60·2% in the needle and syringe group (appendix). Before vaccination, participants had high seroprotection rates against both A strains (about 80% had titres 40). However, only 20% had titres 40 for the B strain before vaccination (appendix).

Participants in the jet injector group reported more immediate complaints (table 2) and more solicited adverse events (days 0–6, p<0·001) than did those in the needle and syringe group. These adverse events were mostly grade 1 or 2 and generally resolved within 3 days.

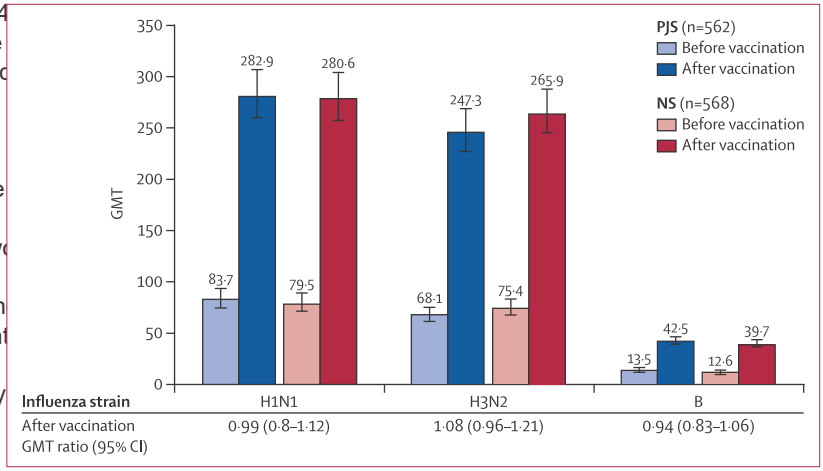

Figure 2: **Geometric mean titres of participants in the immunogenicity population before and after vaccination by study group**
GMT before vaccination equals day 0 and after vaccination equals day 28. GMT ratio is the strain-specific GMT NS group/GMT PJS group. Error bars show 95% CIs. GMT=geometric mean titre. PJS=PharmaJet Stratis needle-free jet injector. NS=needle and syringe.

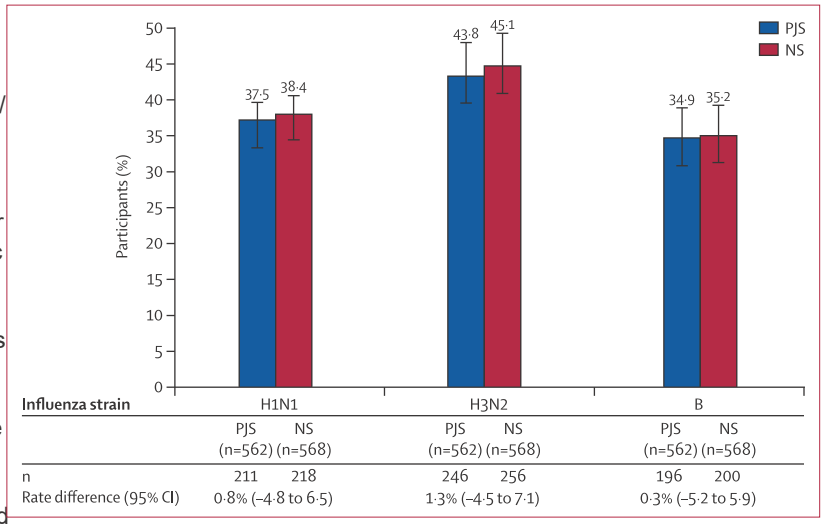

Figure 3: **Seroconversion rates of participants in the immunogenicity population by study group**
The percentage of participants who seroconverted for each virus strain is shown. Seroconversion rate was defined as the proportion of participants with either a haemagglutination inhibition (HI) titre <10 before vaccination and achieving an HI titre ≥40 after vaccination or with an HI titre ≥10 before vaccination and achieving a four-fold or greater increase in HI titre after vaccination. Error bars show 95% CIs. GMT=geometric mean titre. PJS=PharmaJet Stratis needle-free jet injector. NS=needle and syringe.

	PJS group		NS group	
	n/N	%	n/N	%
At least one immediate local reaction (day 0)	295/624	47·3%	107/622*	17·2%
At least one solicited adverse event (days 0–6)	586/616†	95·1%	516/607†	85·0%
At least one spontaneous adverse event (days 0–28)	90/624	14·4%	67/623	10·8%
At least one vaccine-related spontaneous adverse event (days 0–28)	43/624	6·9%	31/623	5·0%
At least one spontaneous severe adverse event (days 0–28)	9/624	1·4%	14/623	2·2%
At least one vaccine-related severe spontaneous adverse event (days 0–28)	3/624	0·5%	4/623	0·6%
At least one serious adverse event	1/624	0·2%	2/623	0·3%

All solicited local reactions were regarded as related to the study procedures. For all solicited systemic adverse events and all spontaneous adverse events, the investigator made a clinical judgment about whether the adverse event was related to the study. The degree of certainty with which an adverse event was attributable to the study or an alternative cause was assessed by the investigator on the basis of three factors: temporal relation to the vaccination or cessation of treatment, reactions of a similar nature previously recorded in the individual or others after needle-free jet injector administration of the vaccine or the vaccine given without the injection device, and safety profiles in the published scientific literature. PJS=PharmaJet Stratis needle-free jet injector. NS=needle and syringe. *Day 0 data were not provided for one participant. †Eight participants in the jet injector group and 16 participants in the needle and syringe group did not return the 7-day diary card.

Table 2: **Safety summary**

	Immediate complaints (≤30 min after vaccination)						Days 0–3 after vaccination						Days 4–6 after vaccination					
	PJS grade ≥1	NS grade ≥1	p value	PJS grade 3	NS grade 3	p value	PJS grade ≥1	NS grade ≥1	p value	PJS grade 3	NS grade 3	p value	PJS grade ≥1	NS grade ≥1	p value	PJS grade 3	NS grade 3	p value
Pain	163/622 (26·2%, 22·8–29·8)	69/622 (11·1%, 8·7–13·8)	<0·001	0/622 (0·0%, <0·1–0·6)	0/622 (0·0%, <0·1–0·6)	NA	397/616 (64·4%, 60·5–68·2)	299/606 (49·3%, 45·3–53·4)	<0·001	5/616 (0·8%, 0·3–1·9)	4/606 (0·7%, 0·2–1·7)	1·00	30/616 (4·9%, 3·3–6·9)	14/606 (2·3%, 1·3–3·8)	0·02	0/616 (0·0%, <0·1–0·6)	0/606 (0·0%, <0·1–0·6)	NA
Tenderness	104/622 (16·7, 13·9–19·9)	36/622 (5·8%, 4·1–7·9)	<0·001	0/622 (0·0%, <0·1–0·6)	0/622 (0·0%, <0·1–0·6)	NA	551/616 (89·4%, 86·7–91·8)	471/606 (77·7%, 74·2–81·0)	<0·001	13/616 (2·1%, 1·1–3·6)	6/606 (1·0%, 0·4–2·1)	0·16	79/616 (12·8%, 10·3–15·7)	25/606 (4·1%, 2·7–6·0)	<0·001	1/616 (0·2%, <0·1–0·9)	0/606 (0·0%, <0·1–0·6)	1·00
Itching	63/622 (10·1%, 7·9–12·8)	17/622 (2·7%, 1·6–4·3)	<0·001	0/622 (0·0%, <0·1–0·6)	0/622 (0·0%, <0·1–0·6)	NA	146/540 (27·0%, 23·3–31·0)	49/527 (9·3%, 7·0–12·1)	<0·001	0/540 (0·0%, <0·1–0·7)	1/527 (0·2%, <0·1–1·1)	0·49	31/540 (5·7%, 3·9–8·0)	8/527 (1·5%, 0·7–3·0)	<0·001	0/540 (0·0%, <0·1–0·7)	0/527 (0·0)	NA
Redness	113/624 (18·1%, 15·2–21·4)	11/621 (1·8%, 0·9–3·1)	<0·001	0/624 (0·0%, <0·1–0·6)	1/621 (0·2%, <0·1–0·9)	0·50	366/609 (60·1%, 56·1–64·0)	115/599 (19·2%, 16·1–22·6)	<0·001	8/609 (1·3%, 0·6–2·6)	2/599 (0·3%, <0·1–1·2)	0·11	65/609 (10·7%, 8·3–13·4)	11/599 (1·8%, 0·9–3·3)	<0·001	1/609 (0·2%, <0·1–0·9)	0/599 (0·0%, <0·1–0·7)	1·00
Swelling	5/624 (0·8%, 0·3–1·9)	0/622 (0·0%, <0·1–0·6)	0·06	0/624 (0·0%, <0·1–0·6)	0/622 (0·0%, 0·1–0·6)	NA	392/605 (64·8%, 60·8–68·6)	118/599 (19·7%, 16·6–23·1)	<0·001	10/605 (1·7%, 0·8–3·0)	1/599 (0·2%, <0·1–0·9)	0·011	54/605 (8·9%, 6·8–11·5)	12/599 (2·0%, 1·0–3·5)	<0·001	2/605 (0·3%, <0·1–1·2)	0/599 (0·0%, <0·1–0·6)	0·50
Bruising	0/623 (0·0%, <0·1–0·6)	0/622 (0·0%, <0·1–0·6)	NA	0/623 (0·0%, <0·1–0·6)	0/622 (0·0%, <0·1–0·6)	NA	104/607 (17·1%, 14·2–20·4)	30/599 (5·0%, 3·4–7·1)	<0·001	1/607 (0·2%, <0·1–0·9)	0/599 (0·0%, <0·1–0·6)	1·00	50/607 (8·2%, 6·2–10·7)	11/599 (1·8%, 0·9–3·3)	<0·001	0/607 (0·0%, <0·1–0·6)	0/599 (0·0%, <0·1–0·6)	NA

Data are n/N (%, 95% CI). The frequency and severity of solicited local reactions after vaccination within 30 min, days 0–3, and days 4–6 are shown. Solicited local reactions were regarded as grade 1 if they did not interfere with activity, grade 2 if they interfered with activity, and grade 3 if they prevented daily activity. Severity grade between treatment groups was compared with Fisher's exact test. 95% CIs were calculated with the Clopper–Pearson (exact) method. NA=not applicable. PJS=PharmaJet Stratis needle-free jet injector. NS=needle and syringe.

Table 3: **Solicited injection site adverse events**

The percentage of participants who reported at least one spontaneous adverse event through day 28 was 14·4% (90/624) for the jet injector group and 10·8% (67/623) for the needle and syringe group (p=0·06). The most frequently reported (≥1% of participants) spontaneous adverse events were injection site erythema (1·4% [9/624] in the jet injector group and 0/623 in the needle and syringe group), injection site haematoma (1·8% [11/624] and 0·2% [1/623], respectively), headache (3·7% [23/624] and 2·2% [14/623] respectively), and oropharyngeal pain (0·5% [3/624] and 1·0% [6/623], respectively). No participants withdrew from the study because of adverse events. Serious adverse events were reported by three participants, none of which were deemed to be related to the study (appendix).

More participants in the needle-free jet injector group reported immediate complaints of pain, tenderness, itching, and redness reported within 30 min after

vaccination than did those in the needle and syringe group; all were grade 1 or 2 except for one report of grade 3 redness in the needle and syringe group (table 3). The differences between treatment groups in immediate reports of pain, tenderness, itching, and redness were significant ($p<0·001$), but reports of swelling and bruising were not significantly different. On days 0–3 and days 4–6, solicited local reactions remained more common in the jet injection group than in the needle and syringe group. The overall severity tended to be greater in the needle-free jet injector group (6·0% [37/616] grade 3) than in the needle and syringe group (3·5% [21/607] grade 3). Fewer local reactions were reported on days 4–6, most resolved within 3 days.

Solicited systemic adverse events were headache, malaise, myalgia, chills, nausea, and vomiting. The occurrence of these adverse events on days 0–3 and days 4–6 was similar in the two groups, with a higher occurrence on days 0–3 that then decreased over time (appendix). Most participants had no fever (ie, temperatures <100·4°F [<38·0°C]) after vaccination (99·7% in both groups; 610/612 needle-free jet injector, 602/604 needle and syringe). Two participants in each group (0·3%) had mild fever; no participants had moderate or severe fever.

Panel: Research in context

Systematic review

On Dec 26, 2013, we searched PubMed for reports published with the terms "influenza vaccine jet injection clinical trial". Between Jan 1, 1979, and Dec 26, 2013, only three clinical trials of liquid influenza vaccine had been published.[17–19] Although findings of these studies show that immunogenicity was similar with the two methods of administration, they were not designed or adequately powered to establish whether administration of influenza vaccine by jet injection was non-inferior to administration by needle and syringe. Additional reports[14] describe the favourable performance of jet injection for administration of various vaccines.

Interpretation

This is the first definitive non-inferiority clinical study of jet injection versus needle and syringe for influenza vaccine delivery. These data support the use of the jet injection device as an acceptable method for administration of Afluria.

Discussion

This is the first definitive non-inferiority study of jet injection versus needle and syringe for influenza vaccine delivery (panel). Findings of previous clinical studies comparing influenza vaccination by jet injection with vaccination by needle and syringe have shown similar immunogenicity with the two methods.[17–19] Additional reports describe the favourable performance of jet injection for administration of various vaccines.[14]

This study used robust endpoints that are recommended by the FDA for accelerated approval for licensure of seasonal influenza vaccines.[13] The jet injection device met the criteria for non-inferiority for both haemagglutination inhibition geometric mean titres and rates of seroconversion for each of the three virus strains contained in the vaccine.

The study population was mainly health-care workers who had previously received annual influenza vaccinations. The prevaccination titres, especially for the A strains, were high, leading to a low rate of sero-conversion. Although the seroconversion rates for the A strains were low, the seroprotection rates after vaccination were very high (>98%). An inverse correlation between titre before vaccination and seroconversion rates has been described previously.[17,29]

Both the jet injection and the needle and syringe methods of administration induced modest responses to the B strain (seroprotection rate 63·7% in jet injection group and 60·2% in needle and syringe group) compared with the A strains (for H1N1, 98·8% in the jet injection group *vs* 98·6% in the needle and syringe group and for H3N2, 98·8% in jet injection group and 98·8% in the needle and syringe group). These results are consistent with bioCSL's 2012–13 yearly re-registration study, which met the European Medicines Agency's Committee for Medicinal Products for Human Use criteria for licensure of annual influenza vaccine formulations.[30] Lower seroconversion to B strains has also been recently reported with other influenza vaccines.[31]

The jet injection device had an acceptable safety and tolerability profile in this study, although we recorded increased rates of local reactions in participants vaccinated with the jet injection device. Jet injection probably leaves trace amounts of vaccine in the layers of the skin as it penetrates to the intramuscular target leading to inflammation and irritation along the injection path.[14] Additionally, jet injection might cause more tissue damage than does needle and syringe. Other clinical studies have also reported that jet injection is associated with a higher frequency of local reactions than is needle and syringe.[14,17,19] We noted no significant difference in systemic adverse events between the two groups. All reported systemic adverse events were consistent with typical influenza vaccination adverse events.

Limitations of this study include the absence of a data and safety monitoring board to oversee the analyses of adverse event causality and the lack of masking of the participants to the method of vaccination. In the setting of a high-volume employee influenza vaccination clinic, masking of participants was impractical. Additionally, participants were health-care workers who, because of their compliance with annual influenza immunization leading to pre-existing immunity, might not provide the same measure of immune responses as a more general population with lower levels of pre-existing immunity. Despite this limitation, the vaccine was immunogenic and the study endpoints were met.

In conclusion, the results from this study support the use of the jet injection device as an acceptable method for administration of Afluria. Moreover, jet injection needle-free administration addresses needle fear and the safety

risks for patients and health-care providers associated with traditional administration of vaccines by needle and syringe. These qualities might contribute to the reduction of barriers to immunisation in the US adult population to help reach CDC goals for annual influenza vaccine coverage.

Contributors

All authors contributed to the study concept and design, and analysed and interpreted data. LM did the literature search, collected clinical data, and approved the report. DKC supervised the study and acquired data. IC and KC provided statistical analyses. LM, JA, DP, and NLCB contributed to the drafting and revision of the report. All authors approved the final version.

Declaration of interests

LM, KC, and PMM are compensated consultants of PharmaJet; JA and DP are employees of bioCSL; KW is an employee of PharmaJet; NLCB was a compensated consultant of bioCSL; IC was a compensated consultant of PharmaJet, a consultant to PATH at the time of study unblinding and analysis, and is currently employed by PATH; and DKC received support from PharmaJet for this study. We declare no other competing interests.

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