Vaccine 37 (2019) 1332–1339

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# Needle-free delivery of influenza vaccine using the Med-Jet® H4 is efficient and elicits the same humoral and cellular responses as standard IM injection: A randomized trial

Janna R. Shapiro [a,b], Breanna Hodgins [a,c], Hilary E. Hendin [a,b], Aakash Patel [a], Karim Menassa [d], Celine Menassa [d], Maurice Menassa [d], Jennifer A. Pereira [e], Brian J. Ward [a,b,f,*]

[a] Research Institute of the McGill University Health Centre, 1001 Decarie St, Montreal, QC H4A 3J1, Canada
[b] Department of Microbiology & Immunology, McGill University, Montreal, QC, Canada
[c] Department of Experimental Medicine, McGill University, Montreal, QC, Canada
[d] Medical International Technologies Canada (MIT Canada), 1872 Beaulac Street, Saint-Laurent, QC H4R 2E7, Canada
[e] JRL Research & Consulting Inc., Toronto, ON, Canada
[f] Vaccine Study Centre, Research Institute of the McGill University Health Centre, Montreal, QC, Canada

ARTICLE INFO

*Article history:*
Received 7 May 2018
Received in revised form 11 January 2019
Accepted 14 January 2019
Available online 29 January 2019

*Keywords:*
Jet injector
Needle-free immunization
Influenza vaccine
Humoral immunity
Cell-mediated immunity

ABSTRACT

*Background:* Needle-free vaccine delivery systems have many potential advantages including increased vaccine compliance and decreased risk of needlestick injuries and syringe reuse. The Med-Jet® H4 is a gas-powered, auto-disabling disposable syringe jet injector. The Med-Jet family of products are currently being used in dermatology, podiatry, pain management and veterinary practices. The objectives of this study were to assess patient attitudes, time-efficiency, safety and immunogenicity of the seasonal influenza vaccine delivered by Med-Jet compared to the traditional needle-and-syringe.
*Methods:* A total of 80 patients were randomized 2:1:1 to receive a commercial trivalent vaccine by Med-Jet or needle injection from a single-dose or multi-dose vial. Patient attitudes were assessed pre-randomization and post-immunization. Safety data were collected for 21 days post-immunization. Efficiency of vaccine administration was measured through a time-and-motion study. Humoral and cellular responses were assessed on Days 0 and 21.
*Results:* Overall, the participants readily accepted Med-Jet vaccination despite greater frequency of transient local reactions (eg: redness, swelling) immediately following immunization. Vaccine administration took slightly longer with the Med-Jet, but this difference decreased over time. Geometric mean hemagglutination inhibition titers, seroconversion and seroprotection rates in the Med-Jet and needle groups were equivalent for all influenza strains in the vaccine. Microneutralization responses were also essentially identical. There were no significant differences between the groups in the frequency of functional CD4 + T cells, memory subset distribution or poly-functionality.
*Conclusions:* These data suggest that the Med-Jet is an acceptable means of delivering seasonal influenza vaccine. The system was attractive to subjects, rapidly learned by skilled vaccine nurses and elicited both humoral and cellular responses that were indistinguishable from those elicited with needle injection. While other studies have assessed the humoral response to jet injection of influenza vaccine, to our knowledge, this study is the first to assess the cellular aspect of this response. (ClinTrials.gov-NCT03150537).



## 1. Introduction

Needle-free immunization systems have been suggested as a strategy to increase compliance with immunization recommendations, deliver vaccines rapidly in emergencies (eg: pandemic influenza) and mitigate the public health impact of needlestick injuries and syringe reuse [1]. The development of safe jet injectors

* Corresponding author. Infectious Diseases and Immunity in Global Health Program, Research Institute of the McGill University Health Centre, 1001 Decarie Blvd., EM2.3219, Montreal, QC H4A 3J1, Canada.
*E-mail address:* brian.ward@mcgill.ca (B.J. Ward).

https://doi.org/10.1016/j.vaccine.2019.01.039
0264-410X/

has been promoted by public health authorities including the Center for Disease Control and the WHO as well as major non-governmental organizations such as PATH and the Bill and Melinda Gates Foundation [2]. Initially developed in the 1860s, jet injectors typically deliver vaccines to targeted tissues through a high-pressure liquid stream [2]. Most modern jet injectors use disposable cassettes to ensure safe delivery [2]. Medical International Technologies (MIT Canada) Inc. has developed a series of jet-injection devices based on low-pressure, gas-powered delivery of an ultra-fine stream (0.11 mm: 6 times smaller than a 30 G needle) of vaccine that minimizes patient discomfort and leakage. Unlike spring-powered jet injectors, the MIT devices use $CO_2$ or compressed air as a power source, yielding more consistent and accurate injections for the lifetime of the device and a magnet to control the delivery pressure that can be adjusted to achieve dermal, subcutaneous and intramuscular deposition of the vaccine antigen. The newest model, the Med-Jet® H4 (Med-Jet), uses disposable cartridges equipped with a piston tip that breaks upon injection, effectively preventing reuse and thus mitigating the risk of cross-contamination. This approach also affords the possibility of manufacturing pre-filled cartridges to maximize efficiency of vaccine delivery.

In the present study, patients were randomized to receive the seasonal influenza vaccine by Med-Jet or by needle-and-syringe from either single- or multi-dose vials. The seasonal influenza vaccine was chosen for this study because it is typically offered in a 'mass vaccination' context. An observer-based time-and-motion study was used to compare the efficiency of these delivery methods, and patient attitudes and beliefs were surveyed pre- and post-immunization. Humoral and cellular immune responses to vaccine delivered by Med-Jet or needle & syringe were assessed.

## 2. Methods

### 2.1. Study design, participants and vaccine

This trial was approved by the McGill University Health Center (MUHC) Research Ethics Committee and was registered at ClinTrials.gov (NCT03150537: May 4, 2017). The 80 subjects planned for the study were recruited and immunized at the McGill Vaccine Study Centre (Montreal, QC) between May 12–18, 2017 and randomized 2:1:1 to be vaccinated by Med-Jet injection or by intramuscular needle & syringe (NS) injection from either a single-dose (NS-SD) or a multi-dose vial (NS-MD). Random numbers were generated using 'R' version R-3.3.3 for Mac OS X. Randomization was performed by the principle investigator and implemented by the vaccine center. The sample size calculations were patterned after a similar study performed using the Pharmajet jet injector to deliver influenza vaccine [3]. In our study, the most interesting comparisons were between the Medjet and any NS group. We calculated that a sample size of 40 volunteers/group would provide 0.90 power at alpha 0.05 (two-sided) to detect >15% differences in the HI seroconversion rates for H1N1 A/California/07/2009 and H3N2 A/Hong Kong/4801/2014 and >20% for B/Brisbane/60/2008 at day 21 after vaccination.

To participate in the study, patients had to be healthy, 18–49 years of age and have a body mass index between 18–32 kg/m$^2$. Patients who had received an influenza vaccine during the 2016–2017 season were excluded. In all groups, the vaccine used was a standard commercial trivalent split-virion product (FluZone™: Sanofi Pasteur, NY) supplied either in single-dose or multi-dose vials that contained 15 μg hemagglutinin (HA) for each of the WHO-recommended strains for the 2016–17 season (ie: H1N1 A/California/07/2009, H3N2 A/Hong Kong/4801/2014 and B/Brisbane/60/2008 viruses). Serum was collected from each patient prior to vaccination and 21 days (d21) post-immunization for serologic measures. To facilitate handling of the peripheral blood mononuclear cells (PBMC), subjects assigned to morning appointments were asked to participate in a sub-study evaluating cell-mediated immunity. Whole ethylenediaminetetraacetic acid (EDTA)-anticoagulated blood was collected from those who consented. All immunologic assays were performed by operators blinded to group assignment. A brief questionnaire about attitudes and beliefs regarding needles and needle-free immunization was completed by all subjects pre- and post-immunization. Safety data (local and systemic adverse events) were collected in person (30 min), daily for 4 days (by diary) and between d5 to d21 (by diary and report at the d21 blood draw).

### 2.2. Vaccine delivery

The MIT Canada jet injectors are licensed by Health Canada, and are commercially available in the European Union, as well as many other countries. The injectors are designed and manufactured in Montreal and are ISO 13485 and ISO 9001 compliant. Nurses were trained to use the Med-Jet and were given an opportunity to practice administering mock vaccine (sterile saline) before the study began. Because pre-filled cartridges are not yet available, sterile cartridges were filled with an adapter attached to a multi-dose vial and screwed into the device immediately prior to use (Fig. 1A). For intra-muscular (IM) delivery, the Med-Jet is set to 200 lb per square inch (psi). Of course, since the mechanism of delivery is an ultrafine stream of the liquid vaccine itself, a small amount of antigenic material is deposited intradermally and subcutaneously even when the injector is powered to deliver most of the vaccine IM. The device is primed by pulling back gently on the trigger and the nozzle of the device is then pressed firmly onto the patient's skin over the deltoid muscle. The vaccine is delivered by pulling back on the trigger. After vaccination, the cartridge is released from the device for disposal.

### 2.3. Time-and-Motion study

A time-and-motion (TM) study was carried out by two trained, independent observers during all injections. The tasks involved in vaccination were divided into three categories: preparing for vaccine administration, vaccine administration and post-vaccination duties. The visual and verbal cues associated with these steps are detailed in Supplemental Table 1. Each observer recorded task-times in seconds using an electronic data collection form that included time-stamp functionality.

### 2.4. Serology

The hemagglutination inhibition (HI) assays and microneutralization (MN) assays were performed as previously described [4] using H1N1 A/California/07/2009-like, and B/Brisbane/60/2008-like viral stocks grown in eggs and H3N2 A/Hong Kong/4801/2014-like grown in Madin-Darby canine kidney (MDCK) cells (National Microbiology Laboratory, Winnipeg, MN). Testing for non-specific hemagglutinating activity was performed prior to the HI assay. Briefly, receptor destroying enzyme (RDE)-treated sera were diluted 1:4 with PBS and 0.5% turkey erythrocytes. If hemagglutination occurred, sera underwent hemadsorption that was repeated until non-specific hemagglutination activity was no longer observed. Seroprotection was defined as achieving HI titers greater or equal to 40. Subjects with a fold-increase in HI titers from d0 to d21 of at least four were considered to have seroconverted.

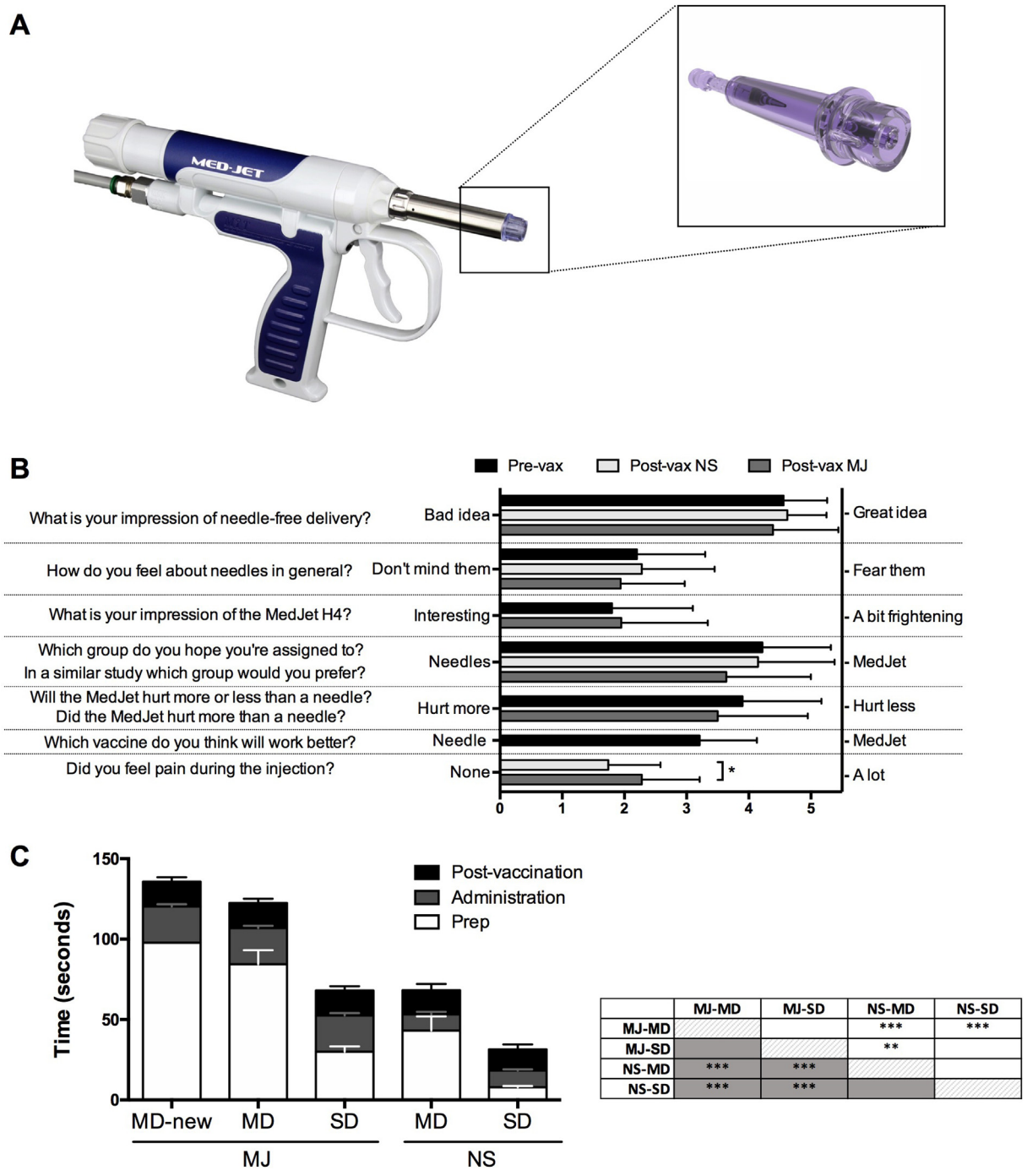


**Fig. 1.** Attitudes, beliefs and time efficiency of Med-Jet vaccine delivery. (A) Med-Jet H4 device used in the study. Enlargement shows cartridge that is loaded with vaccine from a MD vial. (B) Patient attitudes and beliefs about needle-free injection, as determined by a pre-randomization and post-immunization questionnaire. Answers were reported on a 5-point likert scale, and error bars represent the SD. Significance was calculated with a Mann-Whitney test. (C) TM data for each stage of vaccine administration, with 95% CI intervals. MD-new represents time for the first dose from MD vial, when vial adapter had to be attached. The table indicates significance for prep and administration phases. Based on the two-tailed p-values calculated with t-tests, there were no statistically significant differences in the post-vaccine phase.

### 2.5. PBMC isolation & flow cytometry

Peripheral blood mononuclear cells were isolated within 6 h of blood collection by differential density centrifugation and cryopreserved as previously described [5]. Thawed PBMC were plated at 1 million cells per well and either left unstimulated or stimulated with 1.5 μg/mL total HA (0.5 μg/mL HA per strain) of each targeted virus for 18 h. Single-dose Influvac vaccine (Mylan, Maidenhead, UK) was used as the source of viral antigens. After 14 h of stimulation with HA antigen (4h prior to staining), golgi stop and golgi plug (BD, San Jose, CA) were added to each well according to manufacturer's instruction and positive control wells were stimulated with phorbol 12-myristate-13-acetate (PMA) (1.56 μg/mL) and ionomycin (3.125 μg/mL) (Sigma, St. Louis, MO). Cells were stained extracellularly with aqua live/dead viability dye (Invitrogen, Carlsbad, CA), anti-CD4 (clone SK3), anti-CD8 (clone RPA-T8) and anti-CD14 (clone M5E2) (all from BD), and anti-CD27 (clone 0323), anti-CD45RA (clone HI100) and anti-

CCR7 (clone G043H7) (all from Biolegend, San Diego, CA). Cells were then fixed and stained intracellularly with anti-CD3 (clone SP34-2), anti-IFNγ (clone B27), and anti-TNFα (clone 6401.1111) (all from BD), and anti-IL-2 (clone MQ1-17H12) (Biolegend). Samples were acquired on the BD Fortessa X-20. Data were analyzed on FlowJo (TreeStar, version 10.0.8r1) and SPICE (http://exon.niaid.nih.gov/spice) software. The gating strategy used is detailed in Supplemental Fig. 3. HA antigen-stimulated samples for which <100,000 events were acquired were excluded from further analysis. For analysis that included both d0 and d21, six samples from the Med-Jet group and four samples from the NS group were excluded on this basis. Final analysis was performed on twelve subjects from the Med-Jet group and seven subjects from the NS group.

### 2.6. Statistical analysis

Statistical analysis was performed on Graphpad Prism (GraphPad Software, version 6.0c, La Jolla, CA) and Stata 10 (Statacorp, College Station, TX). Note that, for immunologic parameters, the two NS groups were combined for analyses.

## 3. Results

### 3.1. Recruitment & vaccine safety

80 participants were recruited to the study and randomized to one of three intervention groups (Table 1). No patients were lost to follow-up between d0 and d21. Body mass index and demographic characteristics were similar between groups, with an even distribution of males and females, a mean age of 30 (±8.96), and the majority of participants (67.5%) identifying as Caucasian/White (Table 1). Both methods of vaccine administration were found to be safe, with no serious adverse events reported in the 21 days post-immunization. Participants in the Med-Jet group experienced greater swelling and redness but not pain within 30 min of vaccination (Table 2). By the evening of d0, similar rates of local and systemic reactions were reported by all participants, and local reactions were generally resolved by d4 post-immunization in all groups.

**Table 2**
Adverse events.

| Adverse effect | Needle | MedJet H4 | Significance |
|---|---|---|---|
| **Redness** mm (% ≥10 mm) | | | |
| Immediate (30 min) | 1.52 (2.5%) | 41.2 (85%) | **** |
| Day 0 (evening) | 14.9 (35%) | 8.73 (35%) | |
| Day 1 | 6.18 (32.5%) | 15.2 (45%) | |
| Day 2 | 9.8 (30%) | 13.8 (35%) | |
| Day 3 | 6.0 (17.5%) | 8.0 (20%) | |
| Day 4 | 2.6 (10%) | 1.70 (5%) | |
| **Swelling** mm (% ≥10 mm) | | | |
| Immediate (30 min) | 0.56 (2.5%) | 14.2 (75%) | **** |
| Day 0 (evening) | 6.33 (25%) | 5.53 (27.5%) | |
| Day 1 | 6.18 (27.5%) | 8.98 (30%) | |
| Day 2 | 4.10 (20%) | 7.15 (25%) | |
| Day 3 | 1.76 (12.5%) | 3.43 (12.5%) | |
| Day 4 | 0.21 (10%) | 0.73 (2.5%) | |
| **Pain** score 1–5 (% ≥score 2) | | | |
| Immediate (30 min) | 0.09 (0%) | 0.22 (10%) | |
| Day 0 (evening) | 0.53 (7.5%) | 0.55 (0%) | |
| Day 1 | 0.53 (7.5%) | 0.50 (7.5%) | |
| Day 2 | 0.23 (2.5%) | 0.23 (0%) | |
| Day 3 | 0.13 (2.5%) | 0.10 (0%) | |
| Day 4 | 0.08 (2.5%) | 0.08 (0%) | |
| **Itching** score 1–5 | | | |
| Immediate (30 min) | 0.03 | 0.08 | |
| Day 0 (evening) | 0.15 | 0.03 | |
| Day 1 | 0.08 | 0.03 | |
| Day 2 | 0.13 | 0.05 | |
| Day 3 | 0.15 | 0.03 | |
| Day 4 | 0.10 | 0.03 | |
| **Systemic (headache, muscles aches, tiredness, nausea)** n (%) | | | |
| Immediate (30 min) | 1 (2.5%) | 7 (17.5%) | |
| Day 0 (evening) | 10 (25%) | 11 (27.5%) | |
| Day 1 | 11 (27.5%) | 12 (30%) | |
| Day 2 | 5 (12.5%) | 6 (15%) | |
| Day 3 | 2 (5%) | 3 (7.5%) | |
| Day 4 | 0 (0%) | 4 (10%) | |
| **Symptoms After Day 4**n (%) | | | |
| Local | 5 (12.5%) | 7 (17.5%) | |
| Systemic | 3 (7.5%) | 3 (7.5%) | |

Local reactions: Two-tailed P-values calculated with Mann-Whitney test (unpaired, non-parametric)
Systemic and D4+: Two-tailed p-values calculated with Fischer's exact test.

### 3.2. Patient attitudes

Participants answered a brief questionnaire pre-randomization and post-immunization exploring their attitudes towards needles and impressions of the Med-Jet. There were no significant differences between mean responses pre- and post- immunization (Fig. 1B). The majority of participants were enthusiastic about the idea of needle-free immunization, were interested in the Med-Jet and thought that it would work just as well as a NS. Most participants hoped to be in the Med-Jet group and thought that the Med-Jet would hurt less than a needle. Post-immunization, those in the Med-Jet group paradoxically reported that jet injection hurt less than their memory of past needle injections, despite having reported higher levels of pain during the Med-Jet injection ($p = 0.0102$). Pain at the injection site was consistent with the higher levels of local redness and swelling immediately following

**Table 1**
Demographic characteristics of study groups.

| Demographics | Needle (SD) | Needle (MD) | MedJet H4 | Total |
|---|---|---|---|---|
| **Participants** n | 19 | 21 | 40 | 80 |
| Male | 9 | 8 | 23 | 40 |
| Female | 10 | 13 | 17 | 40 |
| **Age** | 30.5 ± 9.4 | 27.2 ± 6.9 | 31.0 ± 9.4 | 30.0 ± 8.96 |
| **Race/Culture** n | | | | |
| Caucasian/White | 10 | 17 | 27 | 54 |
| African/Black | 0 | 0 | 3 | 3 |
| Hispanic | 5 | 3 | 10 | 18 |
| Asian | 2 | 0 | 0 | 2 |
| Native American | 1 | 0 | 0 | 1 |
| Other/No answer | 1 | 1 | 0 | 2 |
| **Weight (Kg)** | 73.2 ± 12.6 | 70.3 ± 14.2 | 76 ± 12.7 | 73 ± 13 |
| **BMI** | 25.4 ± 3.7 | 24.4 ± 3.4 | 25.9 ± 3.2 | 25.4 ± 3.4 |

immunization in the Med-Jet group (Table 2). At d21 post-immunization, 56% of those in the Med-Jet group indicated they would prefer to receive vaccinations by jet injection in the future, and another 2.6% were indifferent.

### 3.3. Time-Motion

The time-motion study revealed that the nurses were not as agile delivering the vaccine with the Med-Jet as with a traditional NS. The largest discrepancy between techniques was during vaccine preparation (Fig. 1C), when the mean time to prepare for administration was significantly longer for the Med-Jet (84.39 s [95% CI: 75.60, 93.18]) than for either NS-SD (7.85 s [95% CI: 7.06, 8.64]) or NS-MD (43.16 s [95% CI: 34.30, 52.03], both $p < 0.001$) (Fig. 1C). However, when we eliminated the time to load the vaccine into the cartridge in order to simulate workflow with a pre-filled cartridge, vaccine preparation time decreased to 30 s (95% CI: 26.77, 33.23) which was significantly shorter than the mean time for NS-MD ($p = 0.0011$) (Fig. 1C). Similar to the first stage, the time to administer vaccine was significantly shorter for NS-SD (10.35 s [95% CI: 9.61, 11.09]) and NS-MD (10.08 s [95% CI: 8.55, 11.61]) than for Med-Jet (SD and MD) (22.24 s [95% CI: 20.49, 23.99], both $p < 0.001$) (Fig. 1C). However, the time to perform post-vaccination duties was not significantly longer with the Med-Jet (15.61 s [95% CI: 12.96, 18.26]) than the NS-SD (13.28 s [95% CI: 10.20, 16.36], $p = 0.29$) or NS-MD (14.95 s [95% CI: 11.00, 18.91], $p = 0.77$) (Fig. 1C). Despite the longer initial vaccination time, the time for each task generally decreased over the five days of vaccinations, indicating a rapid learning curve for nurses adopting this new technology (Supplemental Fig. 1).

### 3.4. Serology

The HI titers (GMT) for the three virus strains increased significantly between d0 and d21 in both the NS and Med-Jet groups and there were no significant differences between the groups for any outcome including the mean GMTs, seroprotection rates (SPR) and seroconversion rates (SCR) (Fig. 2A–C). When HI seroconversion to the individual vaccine antigens was considered (Fig. 2D), 72.5% of the Med-Jet group responded to $\geq$2 vaccine strains compared to 67.5% of the NS group. Only 7.5% of the Med-Jet group failed to respond to any antigen compared to 17.5% of the NS group. Microneutralization titres also rose significantly between d0 and d21 in both groups for all three viruses and, again, there were no statistically significant differences between the NS and Med-Jet groups (Supplemental Fig. 1).

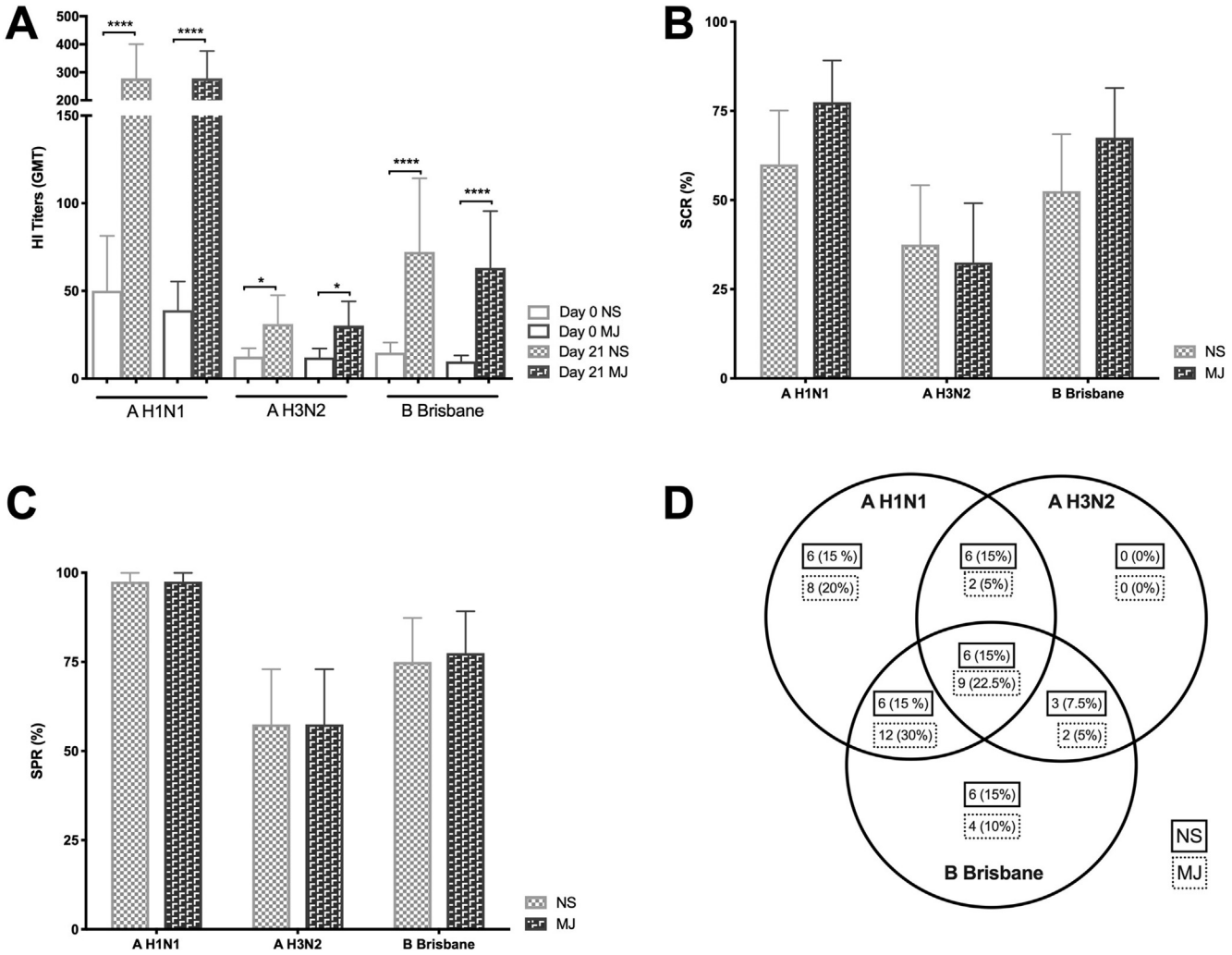


**Fig. 2.** Sera HI response to Influenza vaccine. Serum HI antibody responses to the three viruses in the TIV (H3N2 A/HongKong/4801/2014, B/Brisbane/60/2008 and H1N1 A/California/07/2009) at day 0 and day 21 post-vaccination administered with either NS or Med-Jet. (A) Geometric mean titer (GMT), (B) percent of seroconversion rate (SCR) and (C) percent of seroprotection rate (SPR) (N = 40 for both groups) error bars depict 95% CI. (D) The number (%) of patients in the NS and MJ groups that seroconverted to each of the three antigens contained in the influenza vaccine administered. Tukey tests for multiple comparisons and Fisher's Exact T-tests were used to calculate two-tailed p-values.

### 3.5. CMI

The subset of subjects from whom PBMC were collected (n = 31) had similar demographic and physical characteristic to those who did not participate in the CMI sub-study. Both the number and functionality of $CD4^+$ T cells contribute to protection against viral infections such as influenza [6–8]. We therefore assessed detailed $CD4^+$ T cell responses after *ex-vivo* re-stimulation with HA antigens in a subset of patients. Functional $CD4^+$ cells were defined as expressing any cytokine (IFNγ, TNFα or IL-2) after re-stimulation. The increased frequency of functional $CD4^+$ cells between d0 and d21 was equivalent in both groups (Fig. 3A). Memory cells among the functional $CD4^+$ cell sub-populations were classified as naïve (CD45RA+ CCR7+ CD27+), central memory (CM: CD45RA− CCR7+ CD27+), transitional memory (TM: CD45RA− CCR7− CD27+), effector memory (EM: CD45RA− CCR7− CD27−) or effector memory CD45RA+ (TEMRA: CD45RA+ CCR7− CD27±) [9]. At d21, the Med-Jet group had slightly higher proportions of $CD45RA^-$ memory $CD4^+$ T cells sub-populations (CM, EM and TM) compared to the NS, but none of these differences reached statistical significance (Fig. 3B). When adjusted for pre-vaccination values (d21-d0), there were also no significant differences in $CD4^+$ T cell poly-functionality (ie: expression of $\geq$2 cytokines) between the NS and Med-Jet groups (Fig. 3C). However, slightly higher triple-positive ($IFN\gamma^+$ $TNF\alpha^+$ $IL\text{-}2^+$) $CD4^+$ T cells were seen in the NS group and the Med-Jet group had slightly larger single-positive ($IFN\gamma^+$ or $TNF\alpha^+$) sub-populations. At d21 post-vaccination, there was a modest increase from d0 in the proportion of influenza-specific poly-functional $CD4^+$ T cells in both NS and Med-Jet groups, but none of the differences reached statistical significance (Fig. 3D). A similar analysis was repeated in the $CD8^+$ T cell population but no significant differences were found between the NS and Med-Jet groups (data not shown).

## 4. Discussion

Needle & syringe-based vaccine delivery has a long history of success but also has several serious shortcomings. A recent Canadian survey suggests that needle-phobia was the primary reason for non-compliance with immunization recommendations for 7% of parents and 8% of children [10]. Furthermore, the routine use of needles in vaccination programs poses important risks for patients and healthcare workers. The WHO estimates that 3 million occupation-associated needle-stick injuries occur each year [11]. In many low- and middle-income settings, the risk of needle-stick injuries extends well beyond the healthcare setting due to inadequate disposal practices [12]. Furthermore, disposing of sharp waste can be quite costly. Although recent data on the cost of sharps waste is hard to find, a 1990s estimate suggested $0.55-$1.10(US)/Kg for a total cost of ~$450 M/year in the USA [12]. A disposable, needle-free, non-reusable jet injector system that uses a pre-filled vaccine cartridge could address all of these concerns.

Jet injector systems have been a theoretical possibility for many years. Early prototypes were plagued by contamination issues with some disastrous consequences including major outbreaks of iatrogenic hepatitis B [13–15]. The MIT injectors address the issues of 'splash-back' and cross-contamination by working at relatively low-pressure and using disposable cartridges with a piston tip that breaks off after the vaccine has been injected, ensuring single-use. Because immune responses to influenza vaccines are relatively well-characterized, and because jet injectors would be useful during an infectious disease emergency such as an influenza pandemic, several other jet injectors have been investigated for the delivery of influenza vaccines over the last 20 years [3,16,17]. The findings of our study are consistent with these previous trials in both the equivalence of the humoral responses induced and the frequency of transient local reactions such as swelling and redness immediately following immunization. Although more prevalent at this early time point, the local reactions following Med-Jet injection largely dissipated in the hours following immunization. In contrast, local reactions to needle and syringe delivery were slower to develop, peaking on the evening of d0. Following d1, both the severity and prevalence of adverse reactions decreased steadily, and were similar in both groups. The benign nature of these local reactions is suggested by the fact that, despite their frequency, more than half (56%) of the subjects in the Med-Jet arm of our study still favoured Med-Jet over needle delivery in the post-immunization questionnaire. Med-Jet injectors are currently being used in dermatology [18], cosmetics, podiatry, pain management [19] and veterinary practices in several countries including Canada, Japan, South Africa, South Korea.

Although other studies have reported on humoral responses to jet injection of influenza vaccines [3,16,17], we believe that this is the first study to assess whether or not jet injection can also elicit a cell-mediated immune response. Currently available influenza vaccines largely rely on the generation of neutralizing antibodies to mediate protection [20]. In contrast to the relatively short-lived protective efficacy of neutralizing antibodies, both animal and human data suggest that memory $CD4^+$ T cells can contribute to durable protection against heterosubtypic strains [20–22], and that intradermal (ID) delivery of influenza vaccine can influence the generation of this response [23]. Since small amounts of vaccine antigen are deposited ID and subcutaneously along the track of a Med-Jet IM injection, we hoped that vaccination using this device would elicit better cellular responses than deep IM injection. However, we found that NS and Med-Jet administration elicited modest but comparable $CD4^+$ and $CD8^+$ cellular responses in terms of both memory phenotypes and functional status.

Another innovation of this study was the inclusion of a time-motion element that permitted the 'act' of vaccination to be broken-down into discrete segments. We expect that the differences in time between the two delivery methods can be at least partially attributed to the nurses lack of experience with the Med-Jet prior to the study. Our results over the five study days demonstrate that, even during this short period, nurses were able to adapt to using the Med-Jet with increased efficiency (Supplemental Fig. 3). If the cartridge-filling step is removed (ie: were a pre-filled cartridge to become available), vaccine administration was at least as fast with the Med-Jet as NS delivery from a multi-dose vial (Fig. 1C). Furthermore, our time-motion study did not consider the time needed to dispose of 'sharps' waste. With experience and pre-filled cartridges, it is likely that the speed of Med-Jet vaccination could be faster than a multi-dose syringe, and comparable to a single-dose syringes.

This study has several obvious limitations. The first is its relatively small size with only 40 subjects in each of the study arms. Despite its small size, the immune responses elicited were remarkably consistent between the two injection techniques. A second concern is that the study was carried out at the McGill Vaccine Study Centre with highly-skilled vaccination nurses. This setting initially put the Med-Jet at a disadvantage in terms of the speed of administration although the learning curve for Med-Jet injection was rapid. It is not certain that other healthcare professionals who administer vaccines would adapt as rapidly to this novel delivery system.

In conclusion, this study demonstrates that the Med-Jet delivery system performs well in terms of patient attitudes, safety and the immune response elicited by a commercial influenza vaccine. These findings suggest that use of the Med-Jet for seasonal influenza campaigns might increase vaccine up-take while decreasing needle-stick injuries and the transmission of blood-borne diseases.

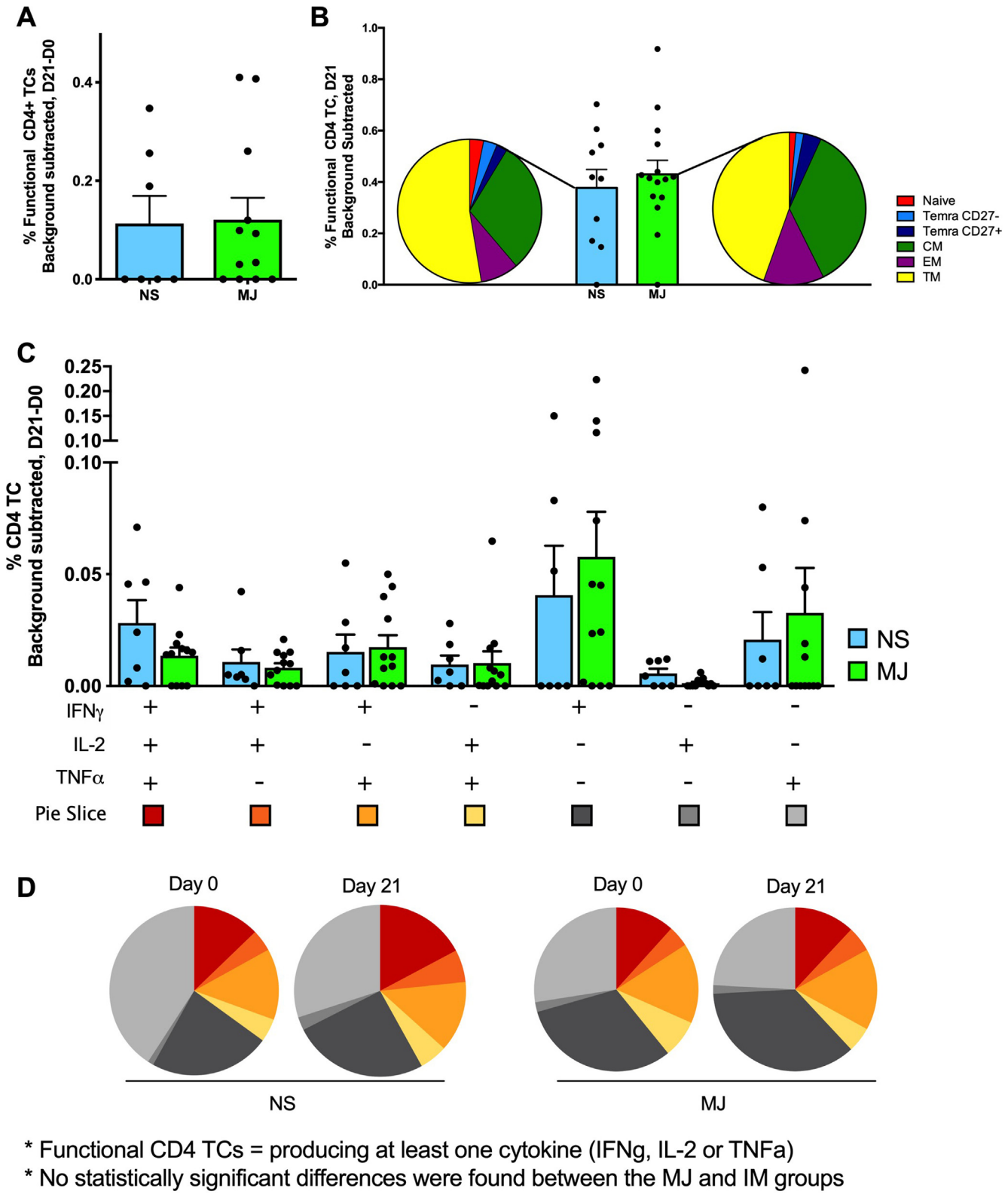


**Fig. 3.** Cell-mediated immune response to influenza vaccine delivered by NS or Med-Jet. PBMCs from D0 and D21 were re-stimulated with trivalent influenza vaccine and stained for memory phenotypes and cytokine production. In bar graphs, the mean + SEM and individual results (dots) are represented, n = 7 for NS group and n = 12 for Med-Jet group. (A) Increase in functional $CD4^+$ TCs (expressing IFNγ, TNFα or IL-2) from D0 to D21. (B) Memory phenotype of functional $CD4^+$ TCs on D21. (C) Qualitative analysis of $CD4^+$ TCs, based on the expression of IFNγ, TNα and IL-2. (D) Relative distribution of 7 cytokine-secreting subsets among functional CD4 + TCs. Based on two-tailed p-values calculated with Mann-Whitney and multiple T-tests, no statistically significant differences were found between the NS and Med-Jet groups.

## Conflicts of interest

JS, BH, HH, AP, JAP and BJW have nothing to disclose. KM is president and CEO of Medical International Technologies Inc. (MIT) Canada, the company that manufactures the Med-Jet. MM and CM are both employees of MIT Canada.

## Acknowledgements

We would like to thank Deirdre McCormack and all the nurses and staff at the MUHC Vaccine Study Centre. We would also like to thank Angela Brewer and Louis Cyr for help processing samples. Thank you to Stephane Pillet for help with flow cytometry experiments.

## Funding sources

JS and BH received funding from Mitacs Accelerate Canada (reference number IT09303). The study was also supported by MEDTEQ-Innovation for Health (project #6-22, injecteur de vaccin, 2017) and Medical International Technologies Canada Inc.

## Contribution of authors

All authors were involved in study design and editing the manuscript. JS and BH performed the time and motion study with guidance from JAP. JS and BH entered data. JS and HH performed flow cytometry experiments. AP performed serology experiments. JS wrote the manuscript with significant editorial help from BH and BJW. All authors have approved the final article.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.01.039.

## References

[1] Levine MM. Can needle-free administration of vaccines become the norm in global immunization? Nat Med 2003;9(1):99.
[2] Weniger BG, Papania MJ. 61 – Alternative vaccine delivery methods A2 – Plotkin, Stanley A. 6th ed. London: W.B. Saunders; 2013. p. 1200–31.
[3] Simon JK et al. Safety, tolerability, and immunogenicity of inactivated trivalent seasonal influenza vaccine administered with a needle-free disposable-syringe jet injector. Vaccine 2011;29(51):9544–50.
[4] Hodgins B et al. A single intramuscular dose of a plant-made virus-like particle vaccine elicits a balanced humoral and cellular response and protects young and aged mice from influenza H1N1 virus challenge despite a modest/absent humoral response. Clin Vaccine Immunol 2017;24(12):e00273–17.
[5] Hendin HE et al. Plant-made virus-like particle vaccines bearing the hemagglutinin of either seasonal (H1) or avian (H5) influenza have distinct patterns of interaction with human immune cells in vitro. Vaccine 2017;35(19):2592–9.
[6] Wilkinson TM et al. Preexisting influenza-specific CD4+ T cells correlate with disease protection against influenza challenge in humans. Nat Med 2012;18:274–80.
[7] Kannanganat S et al. Multiple-cytokine-producing antiviral CD4 T cells are functionally superior to single-cytokine-producing cells. J Virol 2007;81(16):8468–76.
[8] Betts MR et al. HIV nonprogressors preferentially maintain highly functional HIV-specific CD8+ T cells. Blood 2006;107(12):4781–9.
[9] Pillet S et al. A plant-derived quadrivalent virus like particle influenza vaccine induces cross-reactive antibody and T cell response in healthy adults. Clin Immunol 2016;168:72–87.
[10] Taddio A et al. Survey of the prevalence of immunization non-compliance due to needle fears in children and adults. Vaccine 2012;30(32):4807–12.
[11] Prüss-Üstün A, Rapiti E, Hutin Y. Estimation of the global burden of disease attributable to contaminated sharps injuries among health-care workers. Am J Ind Med 2005;48(6):482–90.
[12] Seidman PA, Parker BM. Sharps disposal in the operating room: current clinical practices and costs. Anesth Analg 1998;87(3):634–6.
[13] Control CFD. Hepatitis B associated with jet gun injection–California. MMWR Morb Mortal Wkly Rep 1986;35(23):373.
[14] Zachoval R et al. Risk of virus transmission by jet injection. The Lancet 1988;331(8578):189.
[15] Voelker R. Eradication efforts need needle-free delivery. JAMA 1999;281(20):1879–81.
[16] McAllister L et al. Needle-free jet injection for administration of influenza vaccine: a randomised non-inferiority trial. The Lancet 2014;384(9944):674–81.
[17] Jackson LA et al. Safety and immunogenicity of varying dosages of trivalent inactivated influenza vaccine administered by needle-free jet injectors. Vaccine 2001;19(32):4703–9.
[18] Nantel-Battista M et al. Treatment of nail psoriasis with intralesional triamcinolone acetonide using a needle-free jet injector: a prospective trial. J Cutaneous Med Surg 2014;18(1):38–42.
[19] Benohanian A. Needle-free anaesthesia prior to botulinum toxin type A injection treatment of palmar and plantar hyperhidrosis. Br J Dermatol 2007;156(3):593–6.
[20] Zens KD, Farber DL. Memory CD4 T cells in influenza. Cham: Springer International Publishing; 2015. p. 399–421.
[21] Teijaro JR et al. Memory CD4 T cells direct protective responses to influenza virus in the lungs through helper-independent mechanisms. J Virol 2010;84(18):9217–26.
[22] McKinstry KK et al. Memory CD4(+) T cells protect against influenza through multiple synergizing mechanisms. J Clin Investig 2012;122(8):2847–56.
[23] He X-S et al. Cellular immune responses in children and adults receiving inactivated or live attenuated influenza vaccines. J Virol 2006;80(23):11756–66.