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Comparison of the Immunogenicity and Safety of a Split-virion, Inactivated, Trivalent Influenza Vaccine (Fluzone®) Administered by Intradermal or Intramuscular Route in Healthy Adults

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Abstract

The aim of the study was to determine whether reduced doses of trivalent inactivated influenza vaccine (TIV) administered by the intradermal (ID) route generated similar immune responses to standard TIV given intramuscularly (IM) with comparable safety profiles. Recent changes in immunization recommendations have increased the number of people for whom influenza vaccination is recommended. Thus, given this increased need and intermittent vaccine shortages, means to rapidly expand the vaccine supply are needed. Previously healthy subjects 18-64 years of age were randomly assigned to one of four TIV vaccine groups: standard 15 µg HA/strain TIV IM, either 9 µg or 6 µg HA/strain of TIV ID given using a new microinjection system, (BD Soluvia™

^aBD Soluvia™ is the trade mark of BD micro-injection system, Becton Dickinson (BD), BD Medical Pharmaceutical Systems

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Microinjection Systema), or 3 µg HA/strain of TIV ID given by Mantoux technique. All vaccines contained A/New Caledonia (H1N1), A/Wyoming (H3N2) and B/Jiangsu strains of influenza. Sera were obtained 21 days after vaccination and hemagglutination inhibition (HAI) assays were performed and geometric mean titers (GMT) were compared among the groups. Participants were queried immediately following vaccination regarding injection pain and quality of the experience. Local and systemic reactions were collected for 7 days following vaccination and compared. Ten study sites enrolled 1592 subjects stratified by age; 18-49 years, [N=814] and 50-64 years, [N=778]. Among all subjects, for each of the three vaccine strains, the GMTs at 21 days post-vaccination for both the 9 µg and the 6 µg doses of each strain given ID were non inferior to GMTs generated after standard 15 µg doses/strain IM. However, for the 3 µg ID dose, only the A/Wyoming antigen produced a GMT that was non-inferior to the standard IM dose. Additionally, in the subgroup of subjects 50-64 years of age, the 6 µg dose given ID induced GMTs that were inferior to the standard IM TIV for the A/H1N1 and B strains. No ID dose produced a GMT superior to that seen after standard IM TIV. Local erythema and swelling were significantly more common in the ID groups but the reactions were mild to moderate and short-lived. No significant safety issues related to intradermal administration were identified. Participants given TIV ID provided favorable responses to questions about their experiences with ID administration. In conclusion, for the aggregated cohorts of adults 18 to 64 years of age, reduced doses (6 µg and 9 µg) of TIV delivered ID using a novel microinjection system stimulated comparable HAI antibody responses to standard TIV given IM. The reduced 3 µg dose administered ID by needle and syringe, as well as the 6 µg ID for subjects aged 50-64 years of age generated poorer immune responses as compared to the 15 µg IM dose.

INTRODUCTION

Vaccination against influenza continues to be the major strategy to prevent the disease. Due to the frequent changes in circulating influenza viruses, yearly vaccination is required. The Advisory Committee on Immunization Practices (ACIP) has recommended that all people over 6 months of age, unless there is a medical contraindication, receive yearly immunization against influenza, significantly increasing the number of vaccine doses needed yearly. Increases in the number of influenza vaccine suppliers make it likely that requisite vaccine doses will be available. However, during several recent seasons, vaccine supplies have been compromised raising concern whether sufficient vaccine will consistently meet the demand. [1-4] Intradermal vaccination may facilitate the goal of universal vaccination by sparing the amount of antigen needed and offering an alternative to intramuscular injection. Becton Dickinson has developed a novel system, BD Soluvia™, to test this hypothesis. Accordingly, we designed and conducted a large multicenter study to assess the safety and immunogenicity of TIV administered intramuscularly (IM) as compared to intradermally (ID) using BD Soluvia™ or the Mantoux techniques in a broad range of adult subjects.

MATERIALS AND METHODS

Study Design

This was a multi-center, randomized partially blinded Phase II clinical trial to test the immunogenicity of a single dose of trivalent, inactivated influenza vaccine (TIV) administered either via the intramuscular (IM) route or as reduced antigen doses via the intradermal (ID) route. Each subject was randomly allocated to one of the four treatment groups: the standard 15 µg of each influenza antigen administered IM, 6 µg or 9 µg of each influenza antigen delivered via the BD Soluvia or 3 µg delivered ID using the Mantoux method. The 6 µg and 9 µg dosages were administered using the BD Soluvia in a double blinded manner, while vaccinations administered by the Mantoux method or IM were done in an open label manner. All intradermal dosages were 0.1 mL in volume administered in the

skin of the upper arm while the IM dose was 0.5 mL administered in the deltoid muscle. Immediately post-vaccination, feedback was elicited from subjects regarding acceptability of the method of vaccine administration. Additionally, subjects were required to keep a memory aid for the seven days after vaccination to record pain, erythema and induration at the injection site, and systemic events such as fever, headache, myalgia and malaise. Subjects were provided a caliper and instructed in its use to measure erythema and induration. Participating centers, all National Institutes of Health (NIH) Vaccine and Treatment Evaluation Units (VTEU) or sub-contractors, included Baylor College of Medicine, Cincinnati Children's Hospital Medical Center, Duke University Medical Center, Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Saint Louis University Health Sciences Center, Stanford University School of Medicine, University of Iowa, University of Maryland School of Medicine, University of Rochester, and Vanderbilt University. Vaccinations were performed between November and December 2005 and the study was completed in 2006 at the time of the last six month post-vaccination study phone call.

Subjects

Previously healthy adults 18-64 years of age were enrolled and stratified into two groups (18-49 years of age and 50-64 years of age) with approximately equal numbers of subjects allocated to each of the four vaccine groups. Subjects were excluded if they had a history of immunodeficiency, receipt of blood or blood products within the last 3 months, influenza vaccine within the last 6 months, allergy to components of the vaccine or a condition which, in the opinion of the investigator, may make it unsafe to enroll in the study.

Vaccine

Each 0.5 mL dose of the US licensed influenza vaccine (Fluzone®, 2004-2005 formulation, Sanofi-Pasteur, lot number U1529CA contained 15 µg each of the respective hemagglutinin antigens: A/New Caledonia/20/99 IVR-116 (H1N1), A/Wyoming/03/2003 (H3N2) (an A/Fujian/411/2002-like strain), and B/Jiangsu/10/2003 (a B/Jiangsu/361/2002-like strain). The licensed vaccine was supplied in 5 mL multi-dose vials.

An investigational formulation of two different concentrations (90 µg HA/ml and 60 µg HA/ml) of a split, inactivated, trivalent vaccine containing the same antigens as described above but at higher concentrations than the licensed preparation was prepared by sanofi pasteur and used for the intradermal administration of vaccine. The investigational formulation were supplied in a pre-filled 0.5 mL syringe containing 0.1 mL of vaccine. The investigational formulation was administered using a novel microneedle delivery system (BD Soluvia Microinjection System, Becton-Dickinson, fig 1) designed for intradermal administration resulting in a final dose of 9 µg or 6 µg of each antigen [5, 6]. Both investigators and study subjects were blinded to the dose of investigational formulation of vaccine they received. A third intradermal vaccine group consisted of subjects receiving 0.1 mL dose of the licensed flu vaccine formulation (15 µg/0.5 mL) using the Mantoux method, resulting in receipt of a 3 µg dose of each antigen. All subjects received a single dose of influenza vaccine and were directly observed for 30 minutes following receipt of the vaccine.

Immunogenicity testing

A blood sample was collected from each subject prior to vaccine administration and 21 days later. Serum samples were stored frozen at -20°C and batch shipped to sanofi pasteur where all testing was performed by the same laboratory. Antibody titers against each strain of influenza hemagglutinin were measured using a standard hemagglutination inhibition (HAI) assay beginning at a dilution of 1:10 followed by two-fold serial dilutions (7). The primary

endpoints for the study were the anti-HA antibody geometric mean titers for each antigen in the vaccine obtained 21 days after vaccination.

Secondary endpoints were seroconversion rates (proportion of subjects with a pre-vaccination titer of <10 and a post-vaccination titer of ≥ 40 , or a four-fold increase from a pre-vaccination titer of ≥ 10) and seroprotection rates (defined as the proportion of subjects with a titer ≥ 40 , post-vaccination).

Safety

Safety evaluations included both local and systemic adverse events (AEs) within 30 minutes of injection, and for 21 days following injection (solicited AEs for first 7 days and unsolicited AEs until day 21) and serious adverse events (SAEs) any time during the 6 months after vaccination. Immediate (within 30 minutes of injection) reactions measured included intensity of pain and leakage from the injection site. Solicited AEs during the first seven days after injection included reactogenicity (injection site pain, itching, erythema, and swelling) and systemic complaints of fever, headache, malaise or myalgia.

Pain at injection site and vaccine acceptability

The intensity of pain induced by ID and IM injections was assessed by subjects immediately after vaccination with a Visual Analog Scale (VAS) (17). On a numerical scale of 0 (no pain) to 100 mm (maximal pain induced by injection), one measurement of pain was obtained from each subject. Subjects were also asked to complete an “acceptability questionnaire” after vaccination. The mean values for both the VAS and the questionnaires are presented for each study group.

Evaluation of safety and tolerability of the intradermal route of vaccine administration versus the intramuscular route was the other principal outcome measure. Immediately after receipt of the vaccine, subjects were asked to rate pain of vaccination using a numerical scale as well as complete an “acceptability questionnaire” of the intradermal vaccination.

Sample size Determinations and Statistical Analysis

Sample size was based on a global alpha level of 5% (2.5% one-sided hypothesis for the test of each vaccine group), a clinically relevant difference of 1.5 in terms of post-vaccination GMT (i.e. a difference of $\log_{10}$ (1.5) or approximately 0.176 in terms of $\log_{10}(\text{GMT})$ and a global power of 80.4% (93% for the individual test of each strain). Assuming a maximal standard deviation of 0.67, 344 evaluable subjects were required per vaccine group. Assuming 10% of subjects would be non-evaluable, the final sample size of 382 subjects per vaccine group was used, for a total of 1528 subjects. Within each vaccine group, there were a minimum of 100 subjects in the younger age group and a minimum of 191 subjects in the older age group. After the required minimum number of subjects from each age group was reached, the remainder of the dosage group was filled with any age-eligible subject until the total number of subjects for the vaccine dosage group was reached.

The statistical analysis was performed by EMMES Corporation using SAS software, version 8.2. Each ID vaccine group was compared to the IM group using a non-inferiority testing approach on each strain (A/H3N2, A/H1N1 and B). For each ID group, the difference in the $\log_{10}$ GMTs at 21 days post-dose for the IM and the ID group, $\log_{10}(\text{GMT}_{\text{IM}})$ minus $\log_{10}(\text{GMT}_{\text{ID}})$, and the associated two-sided 95% confidence interval (CI) was computed. If the upper limit of the 95% CI was $<\log_{10}(1.5)$ or approximately 0.176 for each strain, the tested ID group was considered non-inferior to the IM group. Non-inferiority was tested for the entire age group (18-64 years of age) and for each stratified age group (18-49 years and 50-64 years of age). When non-inferiority was demonstrated for a tested ID group, the

superiority of this ID group versus the IM group was tested. If the lower limit of the 95% CI was <0 for each strain, the tested ID group was considered superior to the IM group.

For each vaccine group, an analysis of safety addressed the occurrences of adverse events (AEs) within 30 minutes of injection, local or systemic AEs for 21 days following injection (solicited AEs from D0 to D7 and unsolicited AEs until D21), and serious adverse events (SAEs) any time during the six months after vaccination. The per-protocol analysis set was defined as those subjects who received the vaccination and underwent all blood sampling within study windows. The intent-to-treat analysis included subjects who received the vaccine and provided at least one blood sample. The per-protocol group was used to calculate non-inferiority while the intent-to-treat group was used to test superiority.

RESULTS

Immunogenicity

A total of 1592 subjects, 814 between 18 and 49 years of age and 778 between 50 and 64 years of age, were enrolled in the study, Table 1. Randomization resulted in 398 subjects in the 15 μ g IM group, 395 subjects in the 9 μ g ID group, 399 subjects in the 6 μ g ID group, and 400 subjects in the 3 μ g Mantoux ID group, with an equivalent age distribution within each of the groups. Of the total study subjects, 1591 (99.9%) met criteria for intent to treat and 1571 (98.7%) met criteria for per protocol analysis, and there were no significant differences among the groups (Table 1).

The primary immunogenicity outcome for this study was a comparison of post-vaccination GMTs for the groups receiving TIV intradermally (ID) versus the group that received the vaccine intramuscularly (IM). All vaccine regimens were immunogenic with post-vaccination GMTs significantly higher than the pre-vaccine GMT (Fig. 2a-c). For both the intent to treat and per protocol analysis, the 6 μ g and the 9 μ g ID dose of TIV administered by BD Soluvia™ produced GMTs that were non-inferior to the GMT of the standard 15 μ g IM dose for all 3 vaccine strains, Table 2. Non-inferiority of the 3 μ g ID dose was established only for the A/H3N2 strain. Superiority was not established for any of the 3 strains of influenza in any of the ID groups when compared to the IM group.

Secondary immunological analyses included the percentage of subjects who achieved a post-vaccination HAI GMT $\geq 1:40$ and the percentage that had at least a 4-fold rise in GMT from baseline. For the A/H3N2 flu strain, more than 97% of subjects in all 4 vaccine groups achieved post-vaccination HAI titers $\geq 1:40$, Table 2, and more than 95% of subjects in all 4 vaccine groups achieved post-vaccination HAI titers $\geq 1:80$, data not shown. The percentages of subjects who achieved a post-vaccination HAI GMT $\geq 1:40$ was lower for the other two vaccine strains (A/H1N1, 74-85%; B strain, 65-81%) with the percent responses corresponding to the antigen dose, Table 2. The mean fold rise and seroconversion rates (four-fold or greater rise in post-vaccine GMT) similarly varied by vaccine strains and dosing groups.

Immune response was found to correspond inversely to age, with the percentage of subjects who achieved a post-vaccination HAI $\geq 1:40$ and the GMT responses among subjects 18-49 years of age being significantly greater than for subjects 50-64 years of age for each vaccine strain within each dose group (range $p = 0.01$ to $p < 0.001$) (Table 3, 4). When the immunogenicity data was further analyzed post hoc according to age stratification, results in Table 5 showed that the immune response to the 6 μ g ID dose was non-inferior to the IM control for the 18-49 year age group, but was inferior to IM in the older adult population (50-64 year olds) for 2 of the 3 strains (H1N1 and B strains). While the 9 μ g dose was non-

inferior to IM for all three strains, a slightly lower percentage of subjects in the 9 μ g dose had HAI titers > 1:40 when compared to the 15 μ g group (Tables 2, 6).

Safety Assessments

Reactogenicity, defined as injection site erythema, tenderness, swelling or itching, was common, especially among the subjects receiving an intradermal dose of vaccine (Figure 3). Erythema occurred in 73%, 73%, 74% and 3% in the 3, 6, 9 and 15 μ g groups, respectively, while injection site swelling was reported by 15%, 22%, 27% and 1.3% in the 3, 6, 9 and 15 μ g groups, respectively (Figure 3). Reactogenicity was typically mild or moderate in severity and short lived with the majority resolving within 7 days (Figure 4). Headache was the most frequently reported solicited systemic adverse event overall for subjects in all 4 vaccine groups (27%, 28%, 31% and 25% in the 3, 6, 9, and 15 μ g groups, respectively). Fever occurred in fewer than 1% of subjects in any of the study groups.

Unsolicited AEs were typically of mild severity and most were not associated with the vaccination. One hundred seventy five unsolicited AEs were reported by the 3 μ g group, 170 in the 6 μ g group, 191 in the 9 μ g group and 104 in the 15 μ g group. The most frequently reported unsolicited AEs were headache (occurring after Day 7) followed by URI symptoms (rhinorrhea, congestion) and diarrhea.

Three subjects (1 each in the 3, 9 and 15 μ g groups) reported SAEs during the study period. Only one SAE, which occurred in the subject who received the 9 μ g dose of vaccine intradermally, was thought possibly to be related to study participation. This subject was a 61-year-old white female who, approximately 1 month after being immunized, reported the onset of abdominal pain and increasing bilateral leg weakness which resulted in hospitalization. Initially the subject was diagnosed with transverse myelitis but this was changed to acute disseminated encephalomyelitis based on finding of an enhancing lesion of the left parietal lobe by MRI. The subject was finally diagnosed by her neurologist as having multiple sclerosis and it was the opinion of the neurologist that the subject likely had multiple sclerosis prior to study participation. She remains under his care for this chronic condition and there have been no new exacerbations reported. The event was ongoing at the time of study conclusion.

VAS and Acceptability questionnaires assessments

A majority of subjects reported feeling little or no pain during vaccination. On the scale of 0 (no pain) to 100 mm (maximal pain induced by injection), the mean (95% CI) pain score for subjects in the 3 μ g Mantoux ID group was 21.52 (19.54, 23.50) as compared to 17.19 (15.38, 19.00) in the 6 μ g ID group, 17.31 (15.61, 19.01) in the 9 μ g ID group, and 10.52 (9.14, 11.90) in the 15 μ g IM group. Ninety-seven percent of subjects who received the intradermal injection using the BD Soluvia would be willing to have another vaccination by this method, equivalent to the response of subjects who received the intramuscular vaccination, Table 7.

DISCUSSION

Recurrent episodes of shortage of sufficient influenza vaccine in the recent past and the recent experience with the novel 2009 H1N1 pandemic, have raised interest in ways to expand vaccination to more individuals while using available standard vaccine doses. Previous studies have demonstrated that smaller doses of influenza vaccine (ranging from 3 μ g to 9 μ g of influenza antigen) delivered by either the intramuscular or intradermal route induce immune responses comparable to the standard 15 μ g dose of each antigen delivered intramuscularly [7-11]. Intradermal injection delivers the antigen into the upper layers of the

dermis, an area rich in antigen-presenting cells (APCs) [12-14]. Thus, the ID route of vaccination may enhance the immune response to vaccines. While previous studies of ID administration of influenza vaccine have suggested utility of this route of vaccine delivery, the generalizability of these studies has been limited by sample size of subjects receiving a reduced dose, the route of the decreased dose, differing antigen doses and/or the age of the study subjects. The current study, comparing intradermal to intramuscular administration of trivalent influenza vaccine, utilized a novel system for ID administration and was designed to have sufficient power to determine if dosage, route of administration and/or age were associated with immune responses that were inferior to those when the vaccine in standard dosage is administered intramuscularly.

We demonstrated in the entire study population combined (adults 18-64 years of age), that both the 6 µg and 9 µg doses delivered by the ID route by BD Soluvia™ were non-inferior to a 15 µg dose by the IM route as measured by GMT or seroprotection rates. Neither intradermal dose, however, demonstrated superiority over the IM dose. The 3 µg dose given by Mantoux technique performed less well than either the 6 µg or 9 µg dose, showing non-inferiority to the 15 µg dose only for the A/H3N2 component of the vaccine, to which the majority of subjects already had elevated pre-immunization titers. A limitation of previous dose sparing studies of influenza vaccine has been that study subjects were primarily young adults who may respond to lower doses of vaccine regardless of the route of administration. In an open-label study, Belshe et al [8] compared 119 subjects who received a reduced dose (6 µg) of TIV administered by Mantoux technique to an equal number of subjects vaccinated with standard TIV 15 µg IM. He observed that post-vaccination GMTs were higher among subjects 18-60 years (mean age 40±11) than those of subjects 60 years or older (mean age 70±6), whether intradermal or intramuscular immunization was used. Non-inferiority of GMTs induced by ID administration was reported compared to standard IM administration for the younger age group, but a trend toward a better response in the IM route compared to the ID route was observed for the older age group. These findings are consistent with results from the current study in which TIV was administered intradermally using the BD Soluvia™. GMTs were higher among subjects 18-49 years of age (33.3 ± 8.9 years) than those of the 50-64 year age group (56.2 ± 4.2) regardless of the route (ID or IM). When post-vaccination GMTs were further analyzed according to age stratification, non-inferiority of the 6 µg and the 9 µg ID doses of TIV compared to the 15 µg IM dose was established for all 3 strains of influenza in the 18-49 year age group. However, for the 50-64 year age group, the GMT responses to 6 µg ID formulation were found to be inferior to standard IM dose for 2 of the 3 influenza strains (A/H1N1 and B). Our conclusion is in line with findings of a recent study by Beran et al, (16) who evaluated doses of influenza vaccine ranging from 3 µg to 9 µg administered intradermally (with an earlier version of the microinjection system) compared to a 15 µg intramuscular dose [15]. In the first year of the study, 1150 subjects, 18-57 years of age, were administered either 3 µg or 6 µg intradermal doses or a 15 µg intramuscular dose of TIV. In the following year, subjects in the intradermal groups all received a 9 µg dose because the 3 µg and 6 µg groups in the first year had immune responses statistically lower than the IM group. Subjects receiving the 9 µg ID dose had responses similar to the 15 µg IM dose.

The current study also confirmed a finding from Treanor et al that subjects without a self-reported history of previous receipt of an influenza vaccine within the past 3 years had post-vaccination titers that were higher than the post-vaccination GMTs of subjects who had received a previous influenza vaccine [11]. Due to the large sample size and the multiple doses studied, along with the stratification of dosing by age, we were able to evaluate the post-vaccination GMTs of all these groups according to report of previous receipt of influenza vaccine. While both groups had post-vaccination GMTs as well as seroprotection rates that were high, the difference between those who had received previous influenza

vaccines and those that did not was present in every comparison. Why a previous receipt of an influenza vaccine results in lower post-vaccination GMTs is unclear and likely biologically insignificant, but it may be a factor to consider in the design of future influenza vaccine trials.

Reliability of administering a vaccine into the dermis was another issue addressed in the current study. Subjects in the 6 μ g and 9 μ g ID group were vaccinated using a new injection system specifically designed to reproducibly administer vaccine into the dermis [5, 6, 15]. Study personnel quickly learned to use the intradermal injection system and no issues were noted regarding ability to deliver the vaccine into the dermis. This is in contrast to vaccination via the Mantoux method which requires skilled personnel to reliably deliver a product into the dermis. Another important point regarding intradermal vaccine administration is the acceptability by recipients. More than 97% of subjects given TIV by the BD Soluvia system stated they would be willing to receive another vaccine using the system and 50% stated they thought that vaccination using the BD Soluvia system was less painful than IM flu shots they had received in the past.

An interesting finding was that subjects vaccinated with the BD Soluvia system reported statistically higher average scores by the Visual Analog Scale (VAS) immediately after vaccination (17.19 and 17.31 for the 9 μ g and 6 μ g, respectively) compared to the group who received an IM injection (10.52). However, subjects immunized with the BD Soluvia system reported less pain at the injection site during the 7 day monitoring period (42.7% and 45.6%, respectively) compared to subjects in the IM group (54.0%).

Both the intradermal and intramuscular routes of administration for influenza immunization were well tolerated by subjects. Adverse events were typically mild and short lived. The principal adverse events were related to local reactogenicity, particularly injection site erythema and swelling. These two findings occurred significantly more commonly in the subjects who received intradermal vaccination, with either the BD Soluvia or by Mantoux, as compared to intramuscular injection. It is speculated that delivery of vaccine antigens into the dermis may result in injection site reactions appearing more visible than those associated with IM injection. However, it is important to emphasize that these injection site reactions were transient and resolved spontaneously, with none of them requiring medical intervention. Systemic adverse events were uncommon, mostly judged to be unrelated and occurred with similar frequencies and distribution between the vaccine groups.

A significant limitation of the current study was the lack of a 6 μ g or 9 μ g intramuscular dose group to allow direct comparison to the same dose administered by the intradermal route. A study by Treanor et al suggested half-dose influenza vaccine administered intramuscularly was less immunogenic than the full 15 μ g IM dose [11]. Additionally, a previous study of intradermal administration of influenza vaccine demonstrated lower dosages of vaccine produced post-vaccination GMTs comparable to subjects receiving vaccine intramuscularly [8]. Thus the current study was designed as a larger scale study to only test decreased doses by the ID route as compared to IM administration. Subsequent to the conduct of this study, Belshe conducted a single site study comparing the same dosage administered intradermally and intramuscularly in subjects 18 to 49 years of age [16]. He found that lower doses (3 μ g, 6 μ g or 9 μ g) of vaccine given either intradermally or intramuscularly elicited post-vaccination GMTs nearly equivalent to the 15 μ g IM dose and that the dose response curves over the range of 3 μ g to 15 μ g (IM group) or 3 μ g to 9 μ g (ID group) were nearly flat. They thus concluded that in healthy younger adults, the intradermal vaccination was not superior to intramuscular administration of influenza vaccine. Likely due to the historical decreased immune response in older people, Arnou et al (19, 20) and De Decker et al (21) recently reported use of a 15 μ g dose of influenza vaccine administered ID

using the BD Soluvia as compared to a 15 µg IM dose of vaccine in subjects over 60 years of age and demonstrated a superior immune response in the intradermal group. Thus, while our study was unable to demonstrate superiority of ID vaccination, the results of Arnou et al are intriguing and merit further study to determine if the superiority of the intradermal vaccine can be demonstrated.

In conclusion, reduced doses (6 µg and 9 µg) of TIV delivered ID using a microinjection system provided comparable HAI responses to standard TIV given IM while immune responses to the 3 µg dose administered ID by the Mantoux method were inferior. Whether the ease and reliability of administration using the BD Soluvia outweighs the likely cost increase as compared to using the Mantoux method was not addressed in this study but will need to be considered.

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Fig 1.
The BD Soluvia™ microneedle delivery system

Figure 2.
Reverse Cumulative Distribution of Baseline and Post-vaccination HAI Titers by Vaccine Group

Figure 3.
Percentage of Subjects with Local Reactions by Vaccine Group

Figure 4.
Maximum Local Reactogenicity Per Dose Group by Time After Vaccination

Table 1

Study Demographics

		3 µg ID Mantoux	6 µg ID BD Solvuvia	9 µg ID BD Soluvia	15 µg IM	Total
	n (%)					
Gender						
Female		266 (67)	264 (66)	267 (68)	263 (66)	1060 (67)
Male		134 (34)	135 (34)	128 (32)	135 (34)	532 (33)
Age	n (%)					
18-49		206	205	201	202	814 (51)
50-64		194	194	194	196	778 (49)
Race	n (%)					
White		345 (86)	328 (82)	348 (88)	345 (87)	1366 (86)
Black		27 (7)	36 (9)	22 (6)	31 (8)	116 (7)
Asian		21 (6)	24 (7)	15 (4)	16 (4)	71 (4)
Other		7 (2)	11 (3)	10 (3)	6 (1)	34 (2)
Study Groups by Predefined Analysis	n (%)					
Intent to Treat		400 (100)	399 (100)	394 (99.7)	398 (100)	1591 (99.9)
Per Protocol		395 (98.8)	392 (98.2)	390 (99)	394 (99)	1571 (98.7)

Table 2
Summary of Post-Vaccination HAI Responses By Strain By Vaccine Group (Per Protocol Population)

	N	Pre- vaccination GMT (95% CI)	Pre-vaccination HAI $\geq$ 1:40 n (%)	Post- vaccination GMT (95% CI)	Post- vaccination HAI $\geq$ 1:40 n (%)	Geometric Mean Fold-Rise (95% CI)
A/H3N2						
3 µg ID	395	168.1 (146.9, 192.3)	352 (89.3)	469 (420, 524)	387 (98)	2.80 (2.5, 3.2)
6 µg ID	392	156.6 (137.9, 177.9)	341 (87.2)	566 (511, 628)	391 (99.7)	3.59 (3.1, 4.2)
9 µg ID	390	152.6 (134.2, 173.6)	341 (87.4)	615 (554, 683)	388 (99.5)	4.03 (3.5, 4.7)
15 µg IM	394	154.7 (134.7, 177.8)	344 (87.3)	593 (540, 652)	393 (99.7)	3.83 (3.3, 4.4)
A/H1N1						
3 µg ID	394	32.2 (28.0, 36.9)	179 (45.4)	89 (77, 103)*	291 (74)	2.79 (2.4, 3.2)
6 µg ID	392	29.1 (25.3, 33.5)	166 (42.3)	105 (91, 122)	300 (77)	3.62 (3.1, 4.2)
9 µg ID	390	29.6 (25.7, 34.2)	167 (42.8)	116 (101, 134)	316 (81)	3.92 (3.4, 4.5)
15 µg IM	394	30.1 (26.4, 34.4)	182 (46.2)	121 (106, 138)	336 (85)	4.01 (3.5, 4.6)
B						
3 µg ID	394	17.3 (15.6, 19.1)	108 (27.4)	55 (49, 62)*	255 (65)	3.21 (2.8, 3.6)
6 µg ID	392	16.5 (14.9, 18.2)	105 (26.8)	79 (70, 89)	294 (75)	4.78 (4.2, 5.4)
9 µg ID	390	14.8 (13.5, 16.2)	79 (20.3)	83 (73, 94)	297 (76)	5.59 (4.9, 6.4)
15 µg IM	393	17.6 (15.8, 19.6)	114 (28.9)	87 (78, 97)	320 (81)	4.96 (4.4, 5.6)

* inferior to IM

Table 3
Post-vaccination Seroprotections to Each Component of TIV by Study Group and Age (18-49 yrs vs 50-64 yrs)

Flu Strain	Age Group	3 µg ID Post- vaccination HAI ≥1:40 n (%)	6 µg ID Post- vaccination HAI ≥1:40 n (%)	9 µg ID Post- vaccination HAI ≥1:40 n (%)	15 µg IM Post- vaccination HAI ≥1:40 n (%)
A/H3N2	18-49	198 (97.5)	198 (100)	198 (100)	200 (100)
	50-64	189 (98.4)	193 (99.5)	190 (99.0)	193 (99.5)
	All	387 (98.0)	391 (99.7)	388 (99.5)	393 (99.7)
A/H1N1	18-49	173 (85.6)	180 (90.9)	177 (89.4)	185 (92.5)
	50-64	118 (61.5)	120 (61.9)	139 (72.4)	151 (77.8)
	All	291 (73.9)	300 (76.5)	316 (81.0)	336 (85.3)
B	18-49	146 (72.3)	167 (84.3)	168 (84.8)	175 (87.9)
	50-64	109 (56.8)	127 (65.5)	129 (67.2)	145 (74.7)
	All	255 (64.7)	294 (75.0)	297 (76.2)	320 (81.4)

Table 4
Post-vaccination GMTs to Each Component of TIV by Study Group and Age (18-49yrs vs 50-64 yrs) (Per Protocol Analysis)

Flu Strain	Age Group	3 µg ID GMT (95% CI)	6 µg ID GMT (95% CI)	9 µg ID GMT (95% CI)	15 µg IM GMT (95% CI)
A/H3N2	18-49	543 (464-636)	698 (609-802)	703 (612-808)	711 (623-813)
	50-64	402 (344-469)	457 (394-531)	535 (457-627)	492 (432-561)
	All	469 (420, 524)	566 (511, 627.)	615 (554, 683)	593 (540, 653)
A/H1N1	18-49	153 (125-187)	198 (162-242)	179 (147-217)	192 (162-228)
	50-64	51 (43-61)	55 (47-66)	74 (62-90)	75 (63-89)
	All	89 (77, 103)	105 (91, 122)	116 (101, 134)	121 (106, 138)
B	18-49	71 (60-84)	112 (96-132)	113 (95-134)	109 (94-126)
	50-64	42 (36-50)	55 (46-65)	60 (51-71)	69 (59-80)
	All	55 (49, 62)	79 (70, 89)	83 (73, 94)	87 (78, 97)

Table 5
Analysis of Influenza Post-Vaccination GMTs: 6 µg ID vs. 15 µg IM in Subjects Aged 50 to 64 Years Per-Protocol Population

	Fluzone ID 6 µg (N=194)	Fluzone® 15 µg (N=194)	IM/ID	
Flu Strain	GMT (95% CI)	GMT (95% CI)	GMT Ratio (95% CI)	Non-inferiority
H1N1	55.3 (46.6, 65.6)	75.0 (63.2, 89.0)	1.36 (1.06, 1.74)	No
H3N2	457.4 (394.4, 530.5)	492.2 (431.5, 561.4)	1.08 (0.87, 1.33)	Yes
B	54.6 (46.2, 64.5)	68.9 (59.2, 80.1)	1.26 (1.00, 1.59)	No

* Non-inferiority was established if the upper bound of the 95% GMT Ratio CI was < 1.5.

Table 6
Analysis of Influenza Post-Vaccination GMTs: 9 µg ID vs. 15 µg IM in Subjects Aged 50 to 64 Years Per-Protocol Population

	Fluzone ID 9 µg (N=192)	Fluzone® 15 µg (N=194)	IM/ID	
Flu Strain	GMT (95% CI)	GMT (95% CI)	GMT Ratio (95% CI)	Non-inferiority
H1N1	74.4 (61.6, 90.0)	75.0 (63.2, 89.0)	1.01 (0.78, 1.30)	Yes
H3N2	535.3 (457.2, 626.7)	492.2 (431.5, 561.4)	0.92 (0.75, 1.13)	Yes
B	59.9 (50.6, 71.0)	68.9 (59.2, 80.1)	1.15 (0.91, 1.45)	Yes

* Non-inferiority was established if the upper bound of the 95% GMT Ratio CI was < 1.5.

Table 7
Analysis of Acceptability Questionnaire Results (Safety Population)

Question	6 µg BD-ID n (%)	9 µg BD-ID n (%)	3 µg Mantoux ID n (%)	15 µg IM n (%)
Felt Needle Puncture Skin				
Yes	285 (71)	281 (71)	301 (75)	274 (69)
No	114 (29)	114 (29)	99 (25)	123 (31)
Compared to Regular Flu Shot				
Less/Same Pain	295 (74)	288 (73)	236 (59)	312 (78)
Less painful	199 (50)	195 (49)	117 (29)	105 (26)
Same amount of pain	96 (24)	93 (24)	119 (30)	207 (52)
More painful	41 (10)	33 (8)	84 (21)	6 (2)
No opinion/Don't know	63 (16)	74 (19)	80 (20)	79 (20)
If Offered Another Flu Shot, Receive by Same Method?				
Yes	384 (96)	386 (98)	367 (92)	385 (97)
Yes, Little/No Reservation	362 (91)	366 (93)	332 (83)	370 (93)
Yes, Some/Much Reservation	22 (5)	20 (5)	35 (9)	15 (4)
No	15 (4)	8 (2)	32 (8)	11 (3)