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Predictors of Reactogenicity to Influenza Vaccination by Microneedle Patch or Hypodermic Needle

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Abstract

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By Michele B. Paine

Objectives: To evaluate the determinants of local and systemic reactogenicity after hypodermic needle insertion or microneedle patch application containing inactivated influenza vaccine (IIV) or placebo**. Methods**: The dataset comes from a phase 1 clinical trial from the Microneedle Patch study TIV-MNP2015 (Clinicaltrials.gov identifier NCT02438423) conducted by Emory University and sponsored by NIH and Georgia Institute of Technology in 2015-2016. The dataset contains data on 100 study participants with epidemiological information collected at baseline and clinical and immunological data collected on Days 0, 2 (+1), 8 (+2), 28 (+/-2), 56 (+/-5), and 180 (+/-14) post vaccination. We used regression analysis to examine the effects of variables such as age, sex, BMI, race, ethnicity, prior influenza vaccination, and immunogenicity on reactogenicity. **Results**: Variables such as age and antibody titers measured by geometric mean titers (GMT) at day 28 post vaccination were shown to be associated with local reactogenicity. Factors that were associated with systemic reactogenicity included age, race, prior receipt of a seasonal influenza vaccination, and GMT at day 28. **Conclusions**: Personal, demographic, and immunologic factors can affect reactogenicity after vaccination with microneedle patches. These factors merit further investigation and confirmation with other clinical trial data, as better understanding of reactogenicity has implications for acceptance of new technology like microneedle patches and for vaccination acceptance in general.

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Chapter I

Background

Influenza leads to significant morbidity and mortality. In the US, influenza results in 226,000 hospitalizations and thousands of deaths annually, ranging from 3,349 in the 1986-87 season to 48,614 in 2003-04, with annual differences related to the circulating influenza virus type. . Worldwide, the World Health Organization estimates 3-5 million cases of severe illnesses, and 250,000–500,000 deaths per year due to influenza. Influenza-related mortality and morbidity drastically increase during influenza pandemics[1]. The most effective way to prevent influenza is vaccination. Routine annual influenza vaccination is recommended for all persons aged 6 months and older in the United States [2]. Different formulations and delivery methods of influenza vaccines exist: formulations include IIV (trivalent and quadrivalent), live attenuated quadrivalent influenza vaccine, cell culture-based trivalent IIV and recombinant trivalent hemagglutinin influenza vaccine, and common delivery methods include IIV given via the intradermal route or intramuscular route using the traditional hypodermic needle or biojector. In addition, IIV can be formulated for delivery at the standard dose or at a higher dose for the elderly, to attempt to overcome age-related immune senescence Efficacy of the vaccines varies between 10-60^% [3, 4], depending on individual immune responses and how well the vaccine matches the influenza virus strain type in circulation [5].

Influenza prevention through immunization in adults is hindered by low vaccination coverage (<45%)[6] and high immunization costs (US $6.1 billion annually)

[7]. Two leading factors in the cost of influenza vaccination are administration costs and patient time cost [8]. Although more influenza vaccines are administered annually than the annual total of any other vaccine in the US [9], less than 45% of the population receives the vaccine annually [6]. A systematic review of factors influencing pandemic influenza vaccination of healthcare workers noted that vaccine behavior was affected by lack of time and vaccine access [10], even though influenza vaccines can be given outside healthcare settings such as in workplaces, pharmacies and grocery stores. In pandemic settings, it will be challenging to vaccinate the population at risk in a timely manner using the currently available vaccine administration methods. Therefore, during a pandemic, self-vaccination using non-hypodermic needle methods would increase speed of vaccination by removing the bottleneck of healthcare worker availability and reduce risk of transmission by avoiding concentration of patients at clinics.

Vaccine delivery and microneedles

The most commonly available vaccine delivery methods include intramuscular injection using hypodermic needle, which is limited by patient needle phobia [11] and the need for trained medical personnel for vaccine administration. While most vaccines are administered via hypodermic needle and syringe injection, administration this way requires a trained healthcare provider to both provide the injection and dispose of the subsequent sharps waste [12]. Vaccine administration by minimally trained healthcare workers or by patients themselves, through methods other than hypodermic needle injection, could potentially expand the reach of vaccines and reduce costs associated with vaccination [13]. Alternative routes of vaccination that avoid hypodermic needles

have previously been poorly immunogenic, require live vaccines, utilize bulky devices and/or are unsuitable for self-administration [14, 15]. Novel vaccine delivery methods such as microneedle patches can render influenza vaccination easier and more acceptable to the public by simplifying access to vaccine, and can confer protection equal or superior to that induced by hypodermic needle through conventional intramuscular administration [16].

Microneedles are micron-scale needles that administer vaccine directly into the skin using a simple minimally invasive approach with no sharps waste generated. The microneedles are solid conical structures made of water-soluble excipients that encapsulate the influenza vaccine. The microneedles are painlessly inserted into the skin and left in place for varying amounts of time, depending on the manufacturer and contents. Some protocols call for leaving the microneedle patches in place for mere minutes, while others remain in place for hours [17]. During this time, the microneedles dissolve in the skin, so that upon removal of the patch, the microneedles have disappeared and the sharps-free patch backing can be discarded as non-sharps medical waste. Therefore, vaccination can be carried out as simply as applying a disposable adhesive bandage.

IIV administration by the intradermal route has been approved in Europe [18] and the US [19]. Influenza vaccination using microneedles has been extensively studied in recent years. In a mouse model, microneedle vaccination provided complete protection against lethal infectious challenge after vaccination using influenza A H1N1 and H3N2 strains [20, 21]. Influenza vaccination using a microneedle patch in the guinea pig and the rhesus macaque was similarly effective (unpublished data). In addition to improved

humoral immunity, coated microneedles also induced cellular recall responses, such as MHC II-associated CD4+ T helper cells [22].

Microneedles have been studied for other vaccines as well, including rabies, Bacillus Calmette- Guerin (BCG), West Nile virus, and human papilloma virus (HPV) [16]. There are a number of approved medical and cosmetic products using microneedles currently sold around the world. Soluvia® is a single hollow microneedle that is 1.5 mm long and is attached to a syringe. It is marketed worldwide prefilled with influenza vaccine for intradermal vaccination as IDflu®, Intanza® and Fluzone Intradermal®. Also MicronJet® received FDA clearance as a device in 2012.

Vaccination by microneedle patches is designed to increase patient compliance and access to immunization. In focus group studies of the opinions of the public as well as healthcare professionals, microneedle patches were generally viewed positively compared to hypodermic needle injections [23]. Perceived benefits included reduced pain, tissue damage and risk of infections, as well as possibility for self-administration. Concerns focused on delayed availability of the technology, cost, accurate and reliable dosing, and the potential for misuse.

In separate vaccination surveys associated with hollow microneedle injection of the influenza vaccine, most physicians and the general public preferred microneedles over conventional intramuscular injection largely due to the smaller needle size, as well as the increased immunogenicity of intradermal vaccination [24]. Physicians and patients alike thought that microneedle-based vaccination could increase vaccination coverage rates.

Vaccines are typically injected using a hypodermic needle, a low-cost, rapid and direct way for vaccine delivery. However, hypodermic needles cannot be easily used by patients themselves and patient compliance is further limited by pain and needle-phobia experienced by many patients [11]. Spread of blood borne pathogens by needle re-use is also a major concern, especially in developing countries [25]. Microneedles can be prepared as a low-cost patch that is simple for patients to apply for vaccine delivery targeting the many antigen-presenting cells present in the skin. Influenza vaccination by microneedle patches can greatly improve acceptability and safety of influenza vaccines.

The goal of this clinical trial was to assess the safety and efficacy of IIV administered by MNP and IM. The thesis will focus on assessing the local and systemic reactogenicity events observed after MNP insertion when compared to IM administration and determining which factors are associated with these events. Possible factors include gender, race, age, body mass index (BMI), prior vaccination with IIV, and hemagglutination inhibition assay (HAI) titers over time as well as other immunologic markers. These analyses were not originally part of the analysis plan for this study and are considered exploratory assessments.

Chapter II

Predictors of reactogenicity to influenza vaccination by microneedle patch or hypodermic needle

Michele B. Paine

Abstract

Objectives: To evaluate the determinants of local and systemic reactogenicity after hypodermic needle insertion or microneedle patch application containing inactivated influenza vaccine (IIV) or placebo**. Methods**: The dataset comes from a phase 1 clinical trial from the Microneedle Patch study **TIV-MNP2015** conducted by Emory University and sponsored by NIH and Georgia Institute of Technology in 2015-2016. The dataset contains data on 100 study participants with epidemiological information collected at baseline and clinical and immunological data collected on Days 0, 2 (+1), 8 (+2), 28 (+/-2), 56 (+/-5), and 180 (+/-14) post vaccination. We used regression analysis to examine the effects of variables such as age, sex, BMI, race, ethnicity, prior influenza vaccination, and immunogenicity on reactogenicity. **Results**: Variables such as age and antibody titers measured by geometric mean titers (GMT) at day 28 post vaccination were shown to be associated with local reactogenicity. Factors that were associated with systemic reactogenicity included age, race, prior receipt of a seasonal influenza vaccination, and GMT at day 28. **Conclusions**: Epidemiologic and immunologic factors can affect reactogenicity after vaccination with microneedle patches. These factors merit further investigation and confirmation with other clinical trial data, as better understanding of reactogenicity has implications for acceptance of new technology like microneedle patches and for vaccination acceptance in general.

Introduction

Microneedle patches (MNP) provide an alternative to traditional intramuscular delivery of influenza vaccine that offers multiple potential advantages, including immunogenicity (targeting skin, an immunologically rich site), simplicity (amenable to self-vaccination), cost-effectiveness (reducing costs of vaccine administration, cold chain and sharps waste disposal), and safety (eliminating needle-stick injuries) [17].

Dissolvable MNPs are used in a number of cosmetic products [26] and other MNPs have been in human trials, most notably for administration of parathyroid hormone drugs [27-29]. However, vaccination using MNPs has been studied mostly in animals for delivery of polio, measles, and human papilloma virus in addition to influenza. We conducted a first-in-humans, partially blinded, placebo-controlled, randomized phase 1 clinical trial comparing the safety, reactogenicity and immunogenicity of inactivated influenza vaccine (IIV) delivered using a dissolvable microneedle patch applied by a healthcare worker (HCW) or through self-administration, and compared to traditional delivery by hypodermic needle.

This trial provided an opportunity to explore factors that may influence reactogenicity, including age, BMI, sex, race, ethnicity, past receipt of seasonal influenza vaccine, and immunogenicity. This report documents our analysis of reactogenicity findings from the larger trial. All vaccinations occurred after the end of the 2014-15 influenza season (enrollment June-September 2015). in subjects who previously elected not to receive the vaccine during influenza season.

Methods

Study design and participants

This was a single-center, partially blinded study in which healthy, non-pregnant adults (18-49 years) were equally randomized to one of four groups receiving: IIV by MNP ($MNP_{IIV\text{-}HCW}$); IIV by IM injection (IM_{IIV}); or placebo by MNP ($MNP_{placebo}$), all applied by an unblinded healthcare worker (HCW); or IIV by MNP self-administered by study subjects ($MNP_{IIV\text{-}self}$).

The randomization code was prepared by a pharmacist using Research Randomizer Form V4.0 and provided to an unblinded HCW who was aware of study-group assignments. Subjects were unaware if the MNP applied by the unblinded HCW contained IIV or placebo, and investigators were unaware if MNPs were applied by unblinded HCW or by subjects. MNPs were applied to the dorsal aspect of the wrist of the non-dominant arm. An alcohol wipe was used to sterilize the application site, then allowed to dry before applying the patch. The patch was pushed into the skin until the snap device clicked, indicating enough pressure had been applied, and was then held down for 10 seconds, and then remained in place from 20 minutes before being removed. IM_{IIV} was administered by hypodermic needle in the deltoid muscle, using sterile technique.

At baseline, study staff collected information on the subjects' age, height and weight (to calculate Body Mass Index (BMI)), sex, race, ethnicity, and whether they had received the seasonal flu vaccine in the 2013-2014 or 2012-2013 flu seasons.

After study product administration on day 0, subjects were assessed on days 2(+1), 8(+2), 28(+/-2), 56(+/-5), and 180(+/-14). Solicited injection-site and systemic reactogenicity events were collected by the subject using a memory aid for 7 days after study product administration and, and corroborated by study staff on day 0 post vaccination, day 2 and day 8. Local reactogenicity assessed included swelling, redness, tenderness, pain and itching. Systemic reactogenicity included fatigue, myalgia (muscle pain), shivering/shaking body movements, nausea, headache, arthralgia (joint pain), fever (assessed by measuring temperature with a digital thermometer provided by the clinical trial staff), malaise, and sweating (see Appendix 1). For the local reactogenicity assessment, subjects gave an objective rating from 0 to 3 based on the diameter of redness or swelling, and a subjective rating on pain, tenderness, and itching. Systemic reactogenicity was reported subjectively by the participant, except for fever, which was determined by oral temperature recording. In addition to the diameter of the swelling, subjects could rate subjectively whether the swelling interfered with their daily activities. Unsolicited adverse events were collected by study staff for the first 28 days. Serious adverse events and new onset of chronic medical conditions were collected for the duration of the study. Blood samples were obtained at all time points for safety and/or immunogenicity testing.

All vaccinations occurred after the end of the 2014-15 influenza season in subjects who previously elected not to receive the vaccine during influenza season.

Study products

The licensed 2014-2015 seasonal trivalent influenza vaccine was provided by Novartis® (Cambridge, MA) as single-dose pre-filled syringes and contained the following 3 influenza strains: A/Christchurch/16/2010, NIB-74 (H1N1), A/Texas/50/2012, NYMC X-223 (H3N2), B/Massachusetts/2/2012, NYMC BX-51(B). The MNP was manufactured by the Global Center for Medical Innovation (Atlanta, Georgia) under Good Manufacturing Practices and contained either the excipients with these 3 influenza strains (MNP_{IIV}) or the excipients alone ($MNP_{placebo}$).

MNP were applied to the dorsal aspect of the wrist of the non-dominant arm and left in place for 20 minutes. IIV IM was administered by hypodermic needle in the deltoid muscle. For the $MNP_{IIV\text{-}self}$ group, instructions were provided using audio and poster materials and subjects applied the patch under the unblinded HCW's supervision. Snap devices were placed on the back of MNP to assist with insertion by providing audible feedback to the user when sufficient force was applied. Confirmation of MNP delivery was performed first by the HCW vaccine administrator through visual inspection of both the skin and patch. Used patches were saved and were then inspected under microscope at Georgia Institute of Technology. Some were sent for single radial immunodiffusion (SRID) analysis to determine residual vaccine antigens and thereby calculate the dose delivered by subtraction from loaded dose with the MNP delivering comparable quantities of antigen per strain as IM_{IIV}.

Data Source

Data for this thesis come from the microneedle clinical trial conducted by Emory University and sponsored by NIH and Georgia Institute of Technology in 2015-2016. We conducted convenience sampling to recruit the 100 participants who were subsequently enrolled in the study.

Study variable measurements

At baseline, participants self-reported their gender, race, date of birth, and prior vaccination with IIV in the past 3 years. Height and weight at baseline were recorded by study personnel to calculate BMI. At each visit, a blood sample was taken from each participant for immunologic testing and clinical safety testing. HAI titers were summarized as geometric mean titers, seroprotection rates (i.e., the percentage of subjects with an HAI titer ≥40) and seroconversion rates (i.e., the percentage of subjects with ≥4-fold increase in HAI titer from baseline or a post-vaccination titer ≥40 if the baseline titer was <10). Between day 0 and day 7, participants recorded reactogenicity in a memory aid, using the measures redness, swelling, pain, tenderness, itching, fatigue, myalgia, shivering/shaking, nausea, headache, arthralgia, fever, malaise, and sweating. Study coordinators also took these measures and pictures on days 0, 2 (+1), and 8 (+2). Pictures were taken at each visit that the participant had visible reactogenicity, and at every visit for a subset of participants.

Data analysis

Descriptive data are presented for reactogenicity and immunogenicity. The reactogenicity population included all subjects who received a study product. The immunogenicity population included all subjects who provided serum samples at baseline and at least 28 days after study product administration. The Wilcoxon test was used to compare GMT of each vaccinated group with the placebo group, and Fisher's exact test was used to compare the frequencies of seroprotection and seroconversion between each vaccinated group and the placebo group. The frequencies of reactogenicity events were compared between the four groups using Fisher's exact test. Descriptive statistics were used to characterize and compare each exposure category by sociodemographic information, such as age, sex, race, ethnicity, and previous influenza vaccination in bivariate analyses, using χ 2 and Fisher exact assessments of significance, as appropriate. We also assessed associations between the outcomes of immunogenicity and reactogenicity.

After identifying all relevant factors associated with immunogenicity and reactogenicity through appropriate bivariate analyses, factors significant ($p<0.05$) and feasible were included in a multivariate logistic model. Each multivariate logistic model was assessed for collinearity. Logistic regression was used to investigate the relationship between these variables and the reactogenicity outcomes. Geometric mean titers (GMTs) with 95% confidence intervals were also calculated for variables included in the final model. The relationship between reactogenicity and immunogenicity was investigated by inclusion of the reactogenicity outcomes in the final models. The reactogenicity outcomes were initially considered individually then all significant

variables included together in a model. All statistical analyses were performed using SAS version 9.4 (Cary, NC).

Ethics

The study was approved by Emory University and Georgia Institute of Technology institutional review boards and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

Results

Study subjects

From June 23 through September 25, 2015, 100 subjects were enrolled, underwent randomization and study product administration. There were no significant differences in demographics among the four different groups (Table 1). Three participants in the placebo group missed the day 28 visit and therefore were not included in the immunogenicity population.

Reactogenicity

Local reactogenicity events (Figure 1) that were significantly more common in the MNP/IIV groups than the IM/IIV or MNP/placebo group were: itching (82% vs 16%) (p=0.000001) and redness (40% vs 0%) (p=0.0006). The most common injection site reaction for the two MNP/IIV groups was itching: 87% of these reactions were mild and self-limited, lasting 2-3 days on average. Injection site pain was slightly more frequent

(44% vs 20%; p=0.13) and more severe (≥grade 2) (12% vs 2% p= 0.1) in the IM/IIV group compared to the 2 groups receiving the vaccine by MNP combined. On day 2, pain was less severe in the MNP groups compared to the IM_{IIV} group. The rate and severity of systemic reactogenicity events (Figure 2) did not differ among the 4 groups (p>0.06) except for malaise and fatigue, which was reported more frequently in the IM_{IIV} and $MNP_{IIV\text{-}self}$ groups (p=0.02). Reactogenicity events for the MNP_{IIV} administered by HCW or self-administered by subject were also similar.

Antibody responses

When comparing the three individual IIV groups to placebo, HAI GMT, seroprotection and seroconversion rates at day 28 were statistically higher for all three strains contained in the influenza vaccine (p<0.01). GMT titers for the $MNP_{IIV\text{-}HCW}$ and $MNP_{IIV\text{-}self}$ groups were numerically higher compared to the IM_{IIV} group for the B strains for seroconversion (p=0.01 and p=0.08, respectively) as well as for the GMT for the B strain for the $MNP_{IIV\text{-}HCW}$ group compared to the IM_{IIV} group (p=0.06). MNP containing IIV still provided protection against the 3 influenza strains 6 months after vaccination ($MNP_{IIV\text{-}HCW}$ with 83-100% and $MNP_{IIV\text{-}self}$ 75-100% protection depending on the strains). IM_{IIV} showed 80-100% protection after 6 months, depending on the strain. When compared to placebo, statistical significance was reached mostly for the MNP_{IIV} groups for the H1N1 strain for GMT, seroprotection and seroconversion at D180.

Relationships between reactogenicity and other factors

There was no effect of BMI, sex, race, or prior influenza vaccination on local reactogenicity. Age was significantly associated with the local reactogenicity outcome of pain, with subjects who reported experiencing pain having an average age of 26 years, compared with 30 years of age in those who reported no pain (p=0.02). For the local reactogenicity outcome of redness, day 28 H1N1 GMT were significantly higher in those who experienced redness after vaccination (mean GMT 1,875.6 vs. 1,027.3, p=0.01). Subjects who reported tenderness had significantly higher H3N2 and B strain GMT at day 28 (396 vs. 232 (p=0.02), and 143.6 vs. 98.4 (p=0.02), respectively). For the outcome of any local reactogenicity, the only significant variables were day 28 H3N2 and B strain GMT (p=0.02 and 0.01), with H1N1 GMT at day 28 showing a slight increase (p=0.06).

For systemic reactogenicity, there was no significant effect of BMI, sex, ethnicity, or day 28 B strain GMT. There was a significant association between the outcome of arthralgia and age (those who reported arthralgia had a mean age of 37 years, vs 28.9 in those who did not report arthralgia (p=0.01)). For the outcome of sweating, there was a significant association with the variable race, with subjects who reported their race as “other” reporting significantly less sweating after vaccination than those who reported their race as “white” or “black” (p=0.01). There was an association between the outcome of fatigue and any previous seasonal influenza vaccination (p=0.01). Both the outcomes of headache and fever were associated with higher H3N2 GMT at day 28 (p=0.03 and p=0.004, respectively).

Discussion

This is the first human experience with the use of the single application dissolvable MNP for influenza vaccination. Earlier studies of other microneedle vaccines were limited by the absence of a placebo arm, the use of a metal based microneedle device requiring skilled healthcare care workers (HCW) for administration [30], or the need for 2 injections and prolonged patch wear time (6 hours) [31].

The MNP was well tolerated without any safety signals detected in the phase 1 study though certain local mild self-limited reactions were more commonly observed with MNP/IIV. The higher rates of injection site events are consistent with other vaccinations modalities not involving the traditional hypodermic needle [32, 33] and could reflect local inflammation as part of triggering the appropriate immune response.

This trial was conducted during a period of low seasonal influenza incidence in the United States, to try and decrease the possibility of study participants coming into contact with the influenza virus outside of the study setting.

Individual response to seasonal influenza vaccination can be difficult to predict, and can be due to many different variations between vaccine-recipients [34]. Currently, there is a dearth of information on factors that affect reactogenicity after vaccine receipt. This clinical trial using new vaccine delivery technology provided the opportunity to investigate factors that may predict reactogenicity response after vaccination.

Higher pre-vaccination titers were associated with higher post-vaccination titers for both H1N1 and B strains ($p=0.03$ and 0.001). This could indicate that individuals can still have a good immune response after previous immunization or infection. There was

no association between pre-vaccination titers and reactogenicity. Age was associated with both local and systemic reactogenicity, in particular local pain and systemic arthralgia. In the package insert for the IIV provided by Novartis, they found that elderly (>64 years old) adults experienced pain less frequently than adults aged 18-64, so we may have seen a similar result here even though our population was all under the age of 50.

Previous influenza vaccination was associated with systemic reactogenicity, specifically fatigue. It is possible that having received an influenza vaccination previously and subsequently expecting to experience reactogenicity could be linked.

GMT at day 28 were associated with both local and systemic reactogenicity, which may indicate that increased reactogenicity in the first week after vaccination is associated with a stronger immune response, even as long as 6 months after vaccination. In particular, the finding of the association between fever and increased H3N2 titers at day 28 is consistent with the findings of a 2011 study on reactogenicity in children after receiving an H1N1 vaccine [34].

Strengths and Limitations

These data come from data collected by clinical research staff and by the participants themselves. The sample size of this trial is also relatively small, with only 100 participants. This trial was only partially blinded, as study coordinators were not blinded to whether participants received IM or MNP, but were blinded as to whether the MNP was self-administered or HCW-administered and if the participant received IIV or

placebo. Participants who received the HCW administered patch were blinded to whether they received IIV or placebo. Since reactogenicity was self-reported by the participants and only corroborated by clinical staff on day 0, 2(+1), and 8 (+2), it is possible that participants may have misreported their local and systemic reactions. However, objective measurements were performed by the study staff and pictures of local site reactions were obtained. The grading of some variables, such as itching, is purely subjective. Additionally, it is possible that some of the reactions (particularly systemic) may not have been related to the patch or vaccine. While some grading is subjective, it may still affect acceptability of the patch. To evaluate this, participants completed acceptability questionnaires at baseline, day 0 post-vaccination, day 8, and day 28. Results from the surveys indicated that acceptability of the MNP was high despite increased local reactogenicity, with at least 70% of the participants indicating that they would prefer to receive a MNP for future influenza vaccination.

Conclusions

There is currently little literature on which individual factors may affect reactogenicity after vaccination with the seasonal influenza vaccine. Better understanding the potential association between reactogenicity and the immune response would have immediate practical relevance in vaccine administration. This study provided an opportunity to investigate variables that were associated with greater reactogenicity after vaccination with IIV via either hypodermic needle or the new microneedle patch technology. We found that factors such as sex, ethnicity, and BMI are not good predictors of reactogenicity, while age, race, previous vaccination with the

seasonal influenza vaccine, and immune response may predict reactogenicity. This will allow better counseling for individuals receiving the seasonal influenza vaccination, in addition to providing information that if reactogenicity is present, it may be associated with a better antibody response.

Tables and Figures

Table 1: Demographic characteristics of subjects

Characteristics	IM_{IIV}	$MNP_{IIV\text{-}HCW}$	$MNP_{IIV\text{-}Self}$	$MNP_{Placebo}$	All	p value
Age-year Mean Median Range	 29.64+/- 6.94 29 21-49	 27.36+/-5.92 26 18-43	 31.40+/-8.44 26 22-47	 29.28+/-8.35 26 21-49	 29.42+/-7.51 26 18-49	 0.3054
Sex-no. (%) Male	 14 (56%)	 13 (52%)	 13 (52%)	 13 (52%)	 53 (53%)	 0.9893
Race- no. (%) Caucasian African American Other	 12 (48%) 8 (32%) 5 (20%)	 11 (44%) 8 (32%) 6 (24%)	 14 (56%) 8 (32%) 3 (12%)	 12 (48%) 7 (28%) 6 (24%)	 49 (49%) 31 (31%) 20 (20%)	 0.9463
Ethnicity-no (%) Hispanic	 3 (12%)	 0 (0%)	 2 (8%)	 1 (4%)	 6 (6%)	 0.3148
BMI- kg/m^2 Mean Median Range	 24.9 +/- 4.32 24.8 17.4-34.2	 24.99+/-4.51 24.45 19.24-35.0	 25.68+/-4.01 25.65 18.69-34.21	 24.56+/-4.58 23.82 18.39-34.05	 25.02+/-4.31 24.6 17.1-35.0	 0.8264
Prior IIV 2013-2014 season- no (%) 2012-2013 season-no (%) Any of these 2 seasons-no (%)	 4 (16%) 6 (24%) 8 (32%)	 6 (24%) 3 (12%) 7 (28%)	 7 (28%) 6 (24%) 9 (36%)	 6 (24%) 4 (16%) 9 (36%)	 23 (23%) 19 (19%) 33 (33%)	 0.5725 0.3698 0.9194

Table 2. Reactogenicity by Group

	IM_{IIV}			$MNP_{IIV\text{-}HCW}$			$MNP_{IIV\text{-}Self}$			$MNP_{Placebo}$		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Swelling/Induration	1	0	0	4	0	0	1	1	0	0	0	0
Redness/Erythema	0	0	0	9	1	0	8	2	0	0	0	0
Tenderness	9	6	0	13	4	0	14	1	1	3	1	0
Pain	8	3	0	5	0	0	4	1	0	2	0	0
Pruritis (Itching)	3	1	0	16	3	1	20	1	0	4	0	0
Fatigue	7	2	1	12	1	0	2	2	0	5	0	0
Body ache (Myalgia)	6	1	0	4	0	0	1	0	0	3	1	0
Shivering/ Shaking Body Movements	1	1	0	1	0	0	0	0	0	1	0	0
Nausea	3	1	0	2	0	0	1	1	0	0	1	0
Headache	6	1	0	4	1	0	6	1	0	0	1	1
Joint pain (arthralgia)	1	1	0	0	0	0	2	1	0	1	0	0
Fever	0	0	0	1	0	0	0	0	0	0	0	0
Malaise	2	3	0	4	0	0	0	0	0	1	0	0
Sweating	5	0	0	3	0	0	2	0	0	0	0	0

Table 3. Geometric Mean HAI Antibody Titers Before and After Study Product Administration.

Variable	IM_{IIV}	$MNP_{IIV\text{-}HCW}$	$MNP_{IIV\text{-}self}$	$MNP_{placebo}$
GMT- value (95% CI)				
A/Christchurch (H1N1)				
Day 0	97.14 (62.7, 149.8)	71.27 (44.4, 114.6)	63.5 (39.5, 102)	73.55 (38.0, 142.5)
Day 28	997.3 (703, 1415)	1197 (854.6, 1675)	931.6 (652.4, 1330)	77.52 (39.4, 152.7)
A/Texas (H3N2)				
Day 0	43.47 (30.0, 63.0)	38.86 (25.9, 58.2)	36.68 (23.7, 56.7)	48.32 (33.7, 69.2)
Day 28	223.2 (159.8, 311.7)	287 (191.5, 430.2)	251.6 (162, 390.6)	62.18 (43.2, 89.4)
B/Massachusetts				
Day 0	42.28 (29.3, 60.9)	22.67 (15.2, 33.8)	27.74 (17.0, 45.2)	33.46 (21.3, 52.5)
Day 28	94.48 (73.5, 121.5)	125.8 (85.92, 184.1)	114.2 (86.9, 150.2)	34.53 (21.5, 55.6)
Seroconversion rate- % (95% CI)				
A/Christchurch (H1N1)	80% (59.3-93.2)	92%(73-99)	96%(78.9-99.9)	0%(0-15.4)
A/Texas (H3N2)	76%(54.9-90.6)	83%(62.6-95.3)	75% (53.3-90.2)	14% (3-34.9)
B/Massachusetts	32%(15-53.5)	71% (48.9-87.4)	58% (36.6-77.9)	5% (0-22.8)
Seroprotection rate- % (95% CI)				
A/Christchurch (H1N1)				
Day 0	84%(63.9-95.5)	71%(48.9-87.4)	75% (53.3-90.2)	73%(49.8-89.3)
Day 28	100% (86.3-100)	100% (85,8-100)	100%(85.8-100)	73% (49.8-89.3)
A/Texas (H3N2)				
Day 0	72%(50.6-87.9)	63%(40.6-81.2)	58%(36.6-77.9)	73%(49.8-89.3)
Day 28	100%(86.3-100)	100%(85.8-100)	96% (78.9-99.9)	82%(59.7-94.8)
B/Massachusetts				
Day 0	76%(54.9-90.6)	46% (25.6-67.2)	50% (29.1-70.9)	64%(40.7-82.8)
Day 28	100% (86.3-100)	96%(78.9-99.9)	100%(85.8-100)	64%(40.7-82.8)

Figure 1. Local reactogenicity by group.

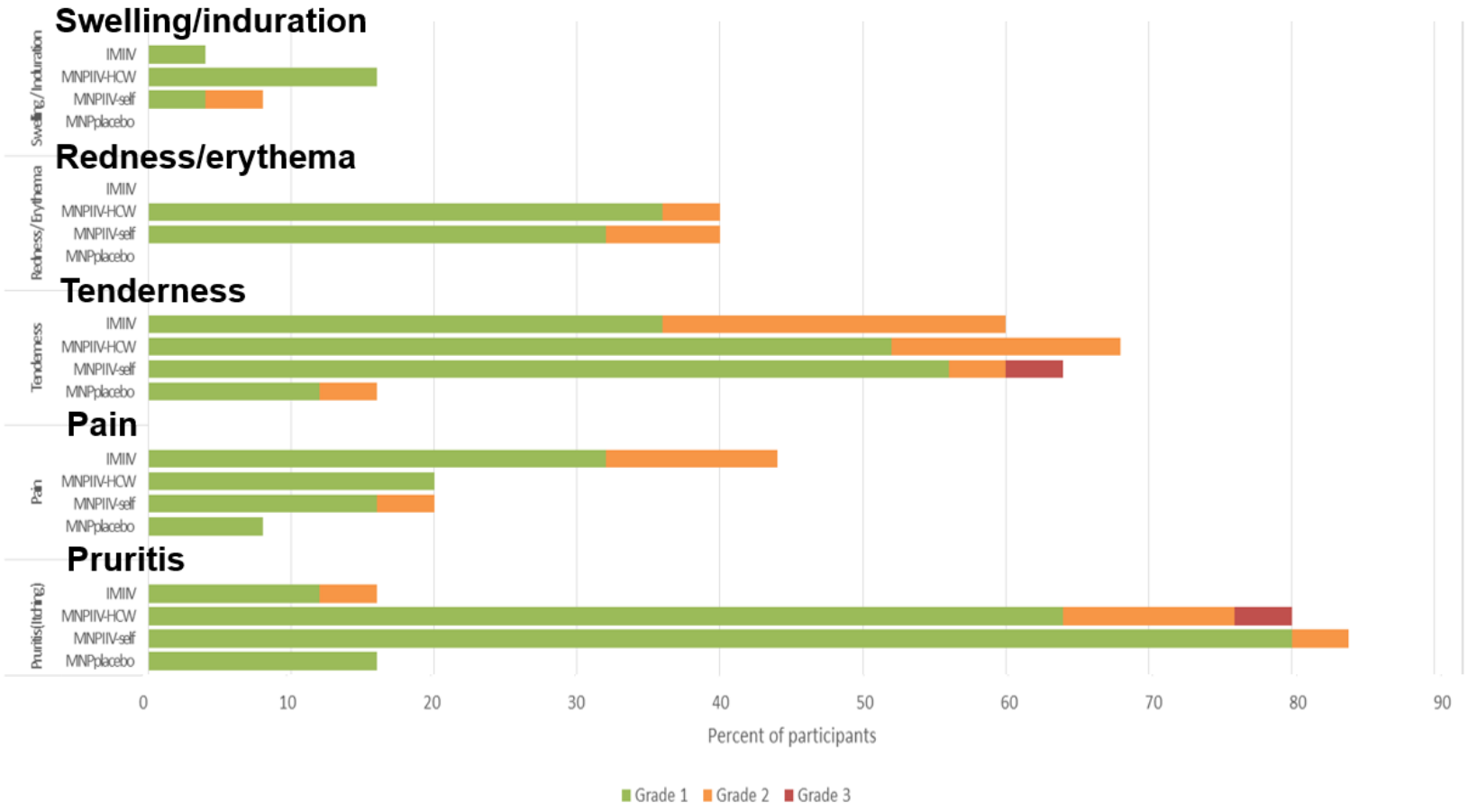
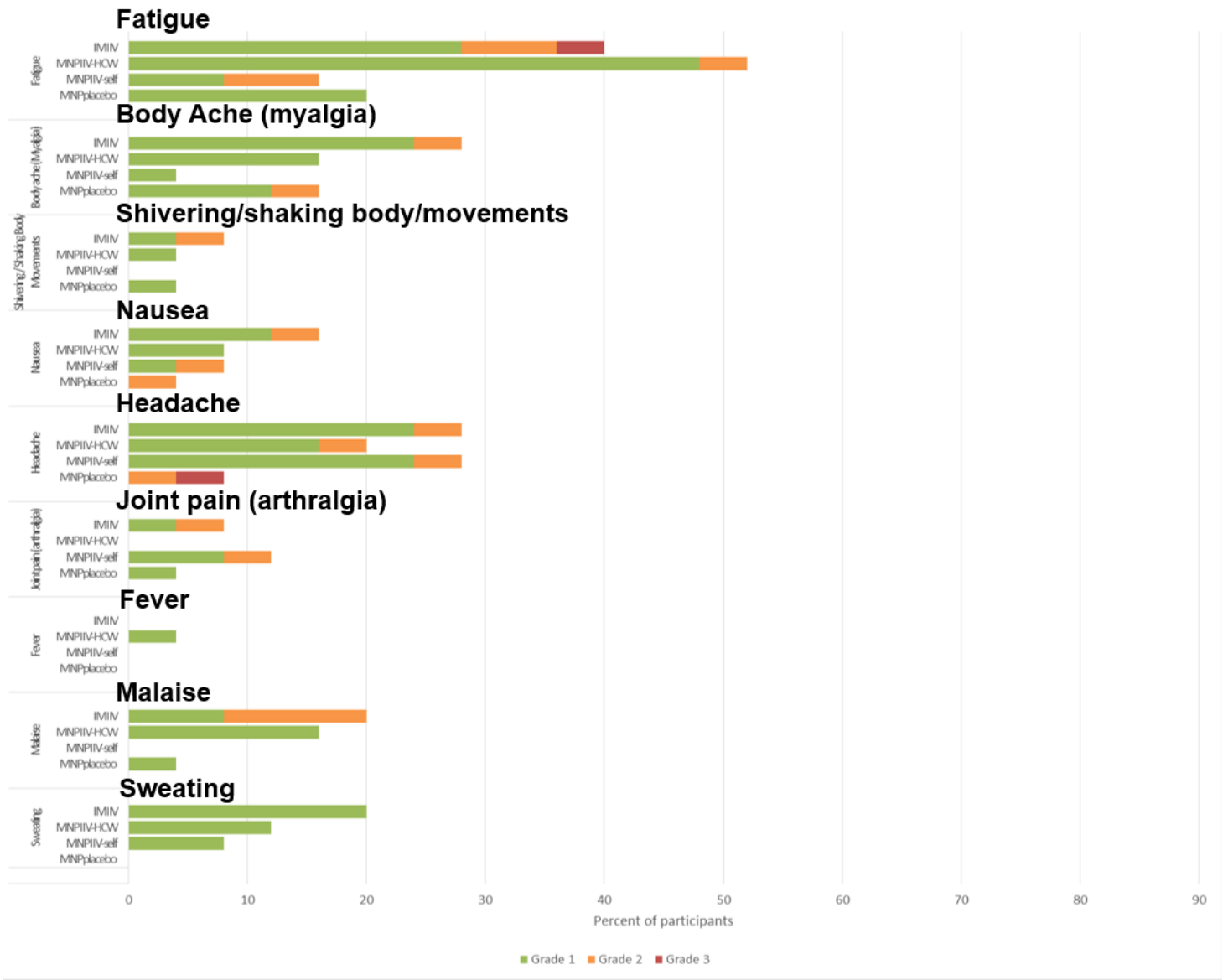


Figure 2. Systemic reactogenicity by group.



Chapter III

Summary

This paper provides some awareness into factors that may influence reactogenicity after vaccination with the seasonal influenza vaccine. In this clinical trial, participants were randomized to receive: IIV by MNP ($MNP_{IIV\text{-}HCW}$); IIV by IM injection (IM_{IIV}); or placebo by MNP ($MNP_{placebo}$), all applied by an unblinded healthcare worker (HCW); or IIV by MNP self-administered by study subjects ($MNP_{IIV\text{-}self}$). Both local and systemic reactogenicity were assessed by both the participant and the study staff during the first week after application. There were differences in reactogenicity between the four groups and in comparing the MNP_{IIV} groups to $MNP_{placebo}$ or to the IM_{IIV} group. Demographic variables that were investigated included age, BMI, sex, race, and ethnicity. We also investigated whether immunogenicity and prior vaccination with a seasonal influenza vaccine could predict reactogenicity. Factors that were associated with increased local reactogenicity included age and immunogenicity (as measured by GMT at day 28). Factors associated with systemic reactogenicity included age, race, previous vaccination with a seasonal influenza vaccine, and immunogenicity at day 28. The effects of various individual factors on reactogenicity merits further investigation and confirmation in other trials. This is to our knowledge the first study that examined these determinants in adults where local reactogenicity could be easily assessed. A 2011 study [34] examined predictors of immunogenicity and reactogenicity in children aged 6 months to 10 years after receiving two doses of an AS03B-adjuvanted split virion or a non-adjuvented whole virion H1N1 (2009) vaccine.

Public Health Implications

In this population, MNPs were well accepted and strongly preferred over traditional IM injection for influenza vaccination, even though local reactogenicity events such as itching and redness were significantly more present in those who received the MNP containing the vaccine. This finding may be significant, because increased acceptability could enable increased rates of influenza vaccination, which are currently less than 50% [6]. Moreover, because subjects were not only able to self-vaccinate, but preferred it in 70% of subjects, there could be significant cost savings enabled by MNPs, due to reduction in HCW time devoted to vaccination. If more research can be done on individual differences that affect reactogenicity, it may be possible to determine which variables are more easily controlled in a vaccination setting.

Influenza vaccination using MNPs was well tolerated, well accepted and resulted in robust immunologic responses, whether administered by HCW or by the subjects themselves. These results provide evidence that MNP vaccination is an innovative new approach with the potential to improve current vaccination coverage, reduce immunization costs, and could improve on immunogenicity. Better understanding of factors that affect reactogenicity may also help to increase vaccination coverage.

Possible Future Directions

We would like to look into his type of research again using a larger sample size to try and analyze a more robust data set, as it is possible that this analysis was not able to detect differences small but still clinically relevant. Additionally, we would like to

look in to factors that are associated with reactogenicity from other vaccines, particularly those with the use of an adjuvant or different types of vaccines.

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Appendices

Appendix 1: Adverse Event & Reactogenicity Grading

Injection Site Reactions

INJECTION SITE REACTIONS					
	Grade				
	0	1	2	3	4
Swelling/Induration*	None	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Redness/Erythema**	None	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Tenderness	None	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Pain	None	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Pruritus (Itching)	None	Mild	Moderate itching; limiting instrumental activities of daily living	Severe itching; limiting self-care activities of daily living	ER visit or hospitalization

*Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement

**In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

General Adverse Reactions

GENERAL ADVERSE REACTIONS					
	Grade				
	0	1	2	3	4
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Body ache (myalgia)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Shivering / Shaking body movements	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Nausea	None	No interference with activity	Some interference with activity	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization
Headache	None	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Joint pain (arthralgia)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Fever	None	38.0 – 38.4 C 100.4 – 101.1 F	38.5 – 38.9 C 101.2 – 102.0 F	39.0 – 40C 102.1 – 104 F	> 40 > 104
Malaise	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Sweating	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization