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Proinflammatory cytokine responses correspond with subjective side effects after influenza virus vaccination

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Abstract

Background—Though typically mild, side effects to the influenza virus vaccine are common and may contribute to negative perceptions including the belief that the vaccine can cause the flu. However, the extent to which subjective symptoms correspond with biological response indicators is poorly understood.

Methods—This study examined associations among subjective side effects (soreness at the site of injection and illness-like symptoms), serum proinflammatory cytokines and body temperature a baseline, 1, 2, and 3 days following receipt of trivalent inactivated influenza vaccine (IIV3) in a sample of 56 women 18–40 years in age.

Results—In relation to local reactions, women reporting being very sore at the injection site at 1 day post-vaccination exhibited greater increases in serum TNF-α and MIF in the days following vaccination compared to those with no or mild soreness. In addition, higher basal body temperature was observed in this group compared to other groups (98.7°F versus 98.0°–98.1°). In relation to systemic reactions, women endorsing illness-like symptoms (headache, fatigue, nausea, sore throat, dizziness, achiness, or mild fever) exhibited marginally higher IL-6 at baseline (p = .

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Conflicts of Interest

The authors report no conflicts of interest.

055) and greater increases in serum MIF at 2 days post-vaccination than those reporting no systemic symptoms. Associations of systemic symptoms with inflammatory responses were not accounted for by concomitant local reactions. As expected, antibody responses to the vaccine were highly similar in women regardless of local or systemic symptoms.

Conclusions—These results are consistent with the notion that subjective reports of local and systemic reactions following vaccination may be predicted by and correspond with biological indicators of inflammatory status, but are not meaningful predictors of antibody responses. To improve adherence to vaccine recommendations, clinicians should provide assurance that such symptoms may be related to normal mild inflammatory responses to the vaccine and do not reflect immunogenicity.

Introduction

Influenza virus vaccine is universally recommended by the Centers for Disease Control and Prevention for all people ≥ 6 months of age. However, only 33–39% of US adults have been vaccinated in recent years [1]. This is well below the *Healthy People 2020* goal of 70% coverage for adults ≥ 18 [2]. Attitudes and beliefs about flu vaccine safety, effectiveness, and possible side-effects are strong predictors of adherence to vaccine recommendations. Commonly reported is concern about getting sick from the vaccine. In the National Flu Survey, 29.6% of adults reported that they were “very/somewhat worried” about getting the flu from flu vaccination [3]. Notably, vaccination rates among those expressing this concern were only 14.4% compared to 42.5% among those who did not.

Side effects related to the vaccine, though typically mild, may contribute to such negative perceptions. Local reactions are common; 50–70% of healthy adults report pain at the injection site, which typically resolves within 2 days [4–6]. In addition, 30–35% report systemic symptoms, such as headache, malagia (muscle aches), malaise, fatigue, and fever [4–7]. However, the extent to which such symptoms correspond to objective biological changes is not clear. Vaccines, including influenza virus vaccine, induce relatively mild and transient inflammatory responses [8–10]. In turn, inflammation is implicated in pain, malaise, fatigue, and general sickness behaviors [11]. Thus, transient inflammatory responses may correspond with subjective symptom reporting.

The current study examined associations among local and systemic subjective side effects and biological indicators of inflammation (body temperature and serum proinflammatory cytokines) prior to and in response to vaccination. This study included 56 women (28 pregnant 28 non-pregnant) who received trivalent inactivated influenza vaccine (IIV3) and were assessed at baseline and 1, 2, and 3 days post-vaccination. It was hypothesized that a more inflammatory profile at baseline as well as a greater inflammatory response to vaccination would predict greater subjective symptoms following vaccination.

2. Methods

2.1. Participants

This was a secondary analyses of data from 56 women (28 pregnant 28 non-pregnant) who were assessed prior to and at 1, 2, and 3 days following receipt of seasonal trivalent

inactivated influenza virus vaccine (IIV3) during the 2011–2012 influenza season. Women were recruited primarily from staff and faculty at The Ohio State University Wexner Medical Center through newsletters and on-line advertisements.

Women were excluded from participation if they reported chronic health conditions with implications for immune or neuroendocrine function including HIV, lupus, arthritis, hypertension, asthma, and diabetes. Women were also excluded if they were taking medications which may alter immune or inflammatory parameters including daily antivirals (e.g., valacyclovir HCl) or statins. Pregnant women were excluded if they reported fetal anomaly or preeclampsia. Women who reported an acute illness with cold or flu like symptoms in the seven days prior to the first study visit were rescheduled. Participants completed written informed consent and received modest compensation for their participation. The study was approved by The Ohio State University Biomedical Institutional Review Board.

2.2. Demographic Measures

Demographic and descriptive information regarding height, current weight, pre-pregnancy weight, age, race, education level, marital status, and income, was collected.

2.3. Influenza Virus Vaccination

Each woman received Fluarix (GlaxoSmithKline) seasonal trivalent influenza virus vaccination. During the 2011–2012 influenza season, each 0.5mL dose contained 45 μg hemagglutinin (HA), with 15 μg HA of each of the following 3 virus strains: A/California/7/09 (H1N1), A/Victoria/361/2011 (H3N2), and B/Wisconsin/1/2010.

2.4. Measures of Inflammatory Response

Body temperature was assessed via medical-grade oral thermometer (WelchAllyn SureTemp Plus) at each study visit. Serum proinflammatory markers were assessed at baseline, 1, 2, and 3 days post-vaccination. At each study visit, whole blood was collected into vacutainer tubes while subjects were in a seated position. On follow-up days, blood samples for the same woman were collected within a 2 hour window of collection of the baseline sample for that particular woman to ensure that sample timepoints were approximately 24 hours apart. Samples were immediately centrifuged, aliquoted, and placed in −80°C freezer storage until analysis. Serum levels of interleukin(IL)-6, tumor necrosis factor (TNF)-α, IL-8, and IL-1β were assayed in duplicate with ultra-sensitive multiplex kits from Meso Scale Discovery (MSD) and chemilluminescence methodology using the Immulite 1000 (Siemens Healthcare Diagnostics, Inc., 1717 Deerfield Rd., Deerfield, Il.). Serum levels of macrophage migration inhibitory factor (MIF) were assayed in duplicate using ultra-sensitive multiplex kits from R&D Systems (Minneapolis, MN) per kit instructions.

2.5. Measurement of Antibody Responses to Vaccination

Serum from baseline and 1 month post-vaccination was assayed using the hemagglutination inhibition (HAI) test. HAI antibody titers reported as <1:10 were valued at 1:5 for statistical purposes. Consistent with prior studies [e.g., 12], seroconversion was defined as a pre-vaccination antibody titer ≤ 1:10 and a post-vaccination titer of ≥ 1:40, or among women

with a pre-vaccination titer >1:10, a 4-fold increase in the titer. Seroprotection was defined as an antibody titer ≥ 1:40.

2.6. Measurement of Subjective Symptoms

Subjective symptoms were recorded at each post-vaccination visit. Women were asked, "How much soreness or pain have you felt in the arm you were vaccinated in since being vaccinated?" with 5 likert-style response options ranging from "Not Sore" to "Extremely Sore". Women were also asked "Have you experienced general achiness, fever, or any other symptoms since being vaccinated?" Those who responded "Yes" were asked to specify the symptoms and rate these as mild, moderate, or severe.

2.7. Statistical Analyses

Descriptive analyses were conducted to determine the frequency of women reporting arm soreness and other symptoms. Chi-square tests were conducted to determine if these rates differed by pregnancy status.

Linear mixed models were used to analyze baseline levels and subsequent trajectories of serum cytokines and body temperature. Comparisons were made based on arm soreness at the day after vaccination, and separately by reporting of systemic symptoms. Contrast estimates within each model were constructed to compare between degrees of soreness or symptom status. All inflammatory marker values were log-transformed for analysis. One participant was excluded from IL-6 and IL-1β analyses due to outlying values.

Finally, we examined antibody responses among women in relation to their reports of local and systemic symptoms. For these analyses, women were dichotomized as experiencing 1) moderate/very sore vs mild/no soreness at the site of injection at 1 day post-vaccination and 2) presence versus absence of systemic symptoms at any timepoint post-vaccination. Women were compared by chi-square analyses or Fisher's Exact Test when necessary, with the antibody response for seroconversion and seroprotection defined as described above.

3. Results

3.1. Demographic and Behavioral Characteristics

Demographic and behavioral characteristics of the study sample are presented in Table 1. Pregnant women were predominately in the 2nd trimester (n = 16; 57%) at the time of vaccination [average weeks gestation = 28.4 (SD = 17.9), range = 11–32 weeks].

3.2. Symptom Reporting

Responses to the subjective symptom questions are shown in Tables 2a and 2b. As shown, the predominant response was mild arm soreness at 1 day post-vaccination (n = 31; 55%), with only 5 (8.9%) endorsing "very sore" (3 pregnant and 2 non-pregnant) and none endorsing "extremely sore". Overall, arm soreness resolved relatively quickly; at 2 days post-vaccination, the majority reported no arm soreness (n = 36; 64%). The majority reported no systemic symptoms following vaccination (n = 44; 78.6%). Ten women reported systemic symptoms at 1 or more post-vaccination assessment; 6 at 1 day post-vaccination

only, 2 at 2 days post-vaccination only, 1 at 3 days post-vaccination only, and 1 woman endorsed symptoms at all 3 post-vaccination assessments. Among these 10 women, the majority reported mild symptoms (n=6) while the remainder reported moderate symptoms (n=4). Symptoms reported, and the frequency of occurrence, were headache (3 occurrences), sleepiness/tired (2), nausea (2), sore throat (2), dizziness (1), mild achiness (1), and mild fever (1). The woman who reported a mild fever at 1 day post-vaccination had a temperature of 99.2° F per oral thermometer, which was the highest recorded temperature in the course of the study.

No significant differences were observed in local (X^2 (3) = 2.8, p = 0.42) or systemic symptoms (X2(1) = 0.49, p = 0.49) based on pregnancy status. In terms of baseline characteristics, non-pregnant women had higher baseline IL-8 (t(53) = 5.91, p < 0.001) and higher baseline MIF (t(54) = 4.96, p < 0.001) than pregnant women. There was no significant difference in baseline IL-6, TNF-a, or IL-1B (ps > 0.11). Pregnant and non-pregnant women did not differ in body temperature at baseline (t(54) = 0.94, p = 0.35). In addition, we have previously reported that, with few modest differences, pregnant and non-pregnant women in this dataset showed similar systemic inflammatory responses in the days following receipt of influenza vaccine [10]. Thus, in further analyses, pregnant and non-pregnant women were examined together. Inclusion of pregnancy status as a control variable did not change any results, including those related to IL-8 and MIF, and this was therefore not included in the model.

3.3. Inflammatory responses and local reactions

In relation to arm soreness, analyses focused on reports of no, mild, moderate, versus very sore in relation to the vaccinated arm at 1 day post-vaccination, as this was the timepoint at which the greatest occurrence and variability in arm soreness was observed (Table 2).

Linear mixed model analyses demonstrated that women reporting moderate arm soreness had lower IL-6 and IL-8 at baseline than those with no soreness (ps < 0.03), and lower IL-8 at baseline than those with mild soreness (p = 0.03). Women reporting they were very sore had higher IL-1β at baseline than those with moderate soreness (p=0.03).

Linear mixed models examining response trajectory showed that, controlling for baseline, women who reported being very sore had higher TNF-α at 1 day post-vaccination than those with mild or no soreness (ps < 0.03) and higher TNF-α at 2 days post-vaccination compared to those with no soreness (p = 0.03; Fig 1). Also, controlling for baseline, women reporting being very sore had higher MIF two days after vaccination compared to those with mild (p = 0.01) or no (p = 0.04) soreness (Fig 1). Controlling for baseline, the very sore group had lower IL-6 2 days post-vaccination than the group with no soreness (p = 0.04; Fig 1).

In relation to body temperature, those with very sore responses had higher temperatures at baseline on average (98.7° F) than those with moderate, mild, or no soreness (98.0°, 98.1°, 98.1° respectively; ps < 0.01; Fig 3a). In addition, at 3 days post-baseline those with no soreness had lower temperatures (97.6°) than those with mild, moderate, or very sore responses (97.9°, 98.0°, 98.1° respectively, ps < 0.04; Fig 3a). In the sample overall,

temperature decreased significantly at 1, 2 and 3 days post-vaccination compared to baseline (ps < 0.003).

3.4. Inflammatory responses and systemic symptoms

Analyses related to symptom reporting examined differences in inflammatory response trajectory among women who reported the presence of systemic symptoms at 1 or more post-vaccination visit (n=10) compared to those reporting no systemic symptoms (n=46). Results showed that those who subsequently experienced systemic symptoms had marginally higher IL-6 at baseline compared to those who went on to experience no symptoms (p = 0.055; Fig 2). In terms of inflammatory response trajectory, controlling for baseline, MIF 2 days post-vaccination was significantly higher in those with systemic symptoms than in those without (p = 0.03; Fig 2). In relation to body temperature, no differences were observed at baseline or in terms of response trajectory among those who experienced symptoms post-vaccination versus not (Fig 3b). Systemic symptom reporting was not significantly associated with reporting of localized pain at the injection site; 10% (1/10) of women with systemic symptoms reported that they were very sore at 1 day post-vaccination compared to 9% (4/46) of women without systemic symptoms ($X^2(1) = 0.02$ p = 0.90).

3.5. Antibody responses and subjective symptoms post-vaccination

As described, antibody levels were measured by HAI at baseline and approximately 1 month post-vaccination. Data at this timepoint were missing for 2 women (1 pregnant, 1 non-pregnant). The majority of women (51/54; 94%) completed this follow-up visit between 27–39 days post-vaccination, with the remaining 3 completing this visit between 43–51 days. Seroconversion and seroprotection, as defined above (Section 2.5), were examined for each of the 3 strains included in the trivalent influenza virus vaccine for the 2011–2012 influenza season (A/California/7/09 (H1N1), A/Victoria/361/2011 (H3N2), and B/Wisconsin/1/2010).

Results showed that women experiencing greater pain at the injection site at 1 day post-vaccination had a significantly lower rate of B seroconversion than women experiencing less pain (46% vs. 76%, p = 0.046; Table 3a). The groups did not differ in B seroprotection or in response to H1N1 or H3N2 strains of the vaccine. In addition, women endorsing systemic symptoms (n = 10) were compared to those reporting no other symptoms (n = 44) (Table 3b). Analyses demonstrated no significant differences between groups in their antibody responses.

Discussion

This study examined the extent to which baseline inflammatory status predicted subjective symptoms and the extent to which subjective symptoms corresponded with objective inflammatory responses in the days following receipt of flu vaccine. We examined these questions in a sample of 56 women, 28 of whom were pregnant.

Beginning with local symptoms of pain at the injection site, we observed some significant differences in baseline serum proinflammatory cytokines. However, these were not consistent across markers or in the direction of effects. In relation to inflammatory responses

post-vaccination, women reporting being very sore exhibited greater increases in serum TNF-α and MIF in the days following vaccination compared to those with no or mild soreness. Controlling for baseline, the very sore group also had lower IL-6 at 2 days post-vaccination than the group with no soreness ($p = 0.04$), which suggests a slightly stronger return toward basal IL-6 levels following an inflammatory response to vaccination. These effects were observed in relation to those endorsing “very sore” responses, step-wise effects with relation to increasing soreness were not observed.

In addition, we found higher basal body temperature among women who subsequently indicated very sore responses at the injection site compared to other groups (98.7°F versus 98.0° – 98.1°). Moreover, at 3 days post-vaccination, women who reported no soreness had significantly lower temperatures than women reporting any soreness. The latter effect was smaller and possibly due to random fluctuation given that the vaccine did not elicit an increase in body temperature overall. In addition, it is notable that in only 1 case was a mild fever of 99.2° recorded. Thus, overall, differences between groups represent variation within a healthy range. This suggests that very subtle differences in underlying physiology may influence vaccine responses in healthy individuals. Of note, differences in body temperature within the normal range have been documented in other contexts with relevance to inflammatory processes including clinical depression and during depressive episodes in bipolar disorder [13, 14]. Together, these data provide some support for the notion that basal inflammatory status and subsequent inflammatory responses correspond with local reactions to vaccination.

Next, we examined systemic symptom. Women who reported systemic symptoms at any time post-vaccination had marginally higher IL-6 at baseline compared to those with no systemic symptoms. In addition, paralleling results in relation to local responses, women reporting systemic symptoms exhibited greater increases in serum MIF at 2 days post-vaccination than those reporting no systemic symptoms. Importantly, associations of systemic symptoms with inflammatory responses were not accounted for by concomitant localized pain; 10% of women who reported systemic symptoms reported very sore local reactions, which was comparable to 9% among women with no systemic symptoms. These results are consistent with the notion that subjective systemic symptoms correspond with biological indicators of inflammatory responses to vaccination.

As anticipated, analyses related to antibody responses demonstrated minimal differences in relation to subjective symptom reporting; women with greater arm soreness were less likely to show seroconversion to influenza B, but did not differ in seroprotection to influenza B. No differences were seen in relation to other strains. In addition, no differences in antibody responses were observed in relation to reporting of systemic symptoms. Thus, the experience of subjective symptoms is not a meaningful predictor of vaccine immunogenicity.

Together, these data indicate that subjective symptoms, particularly local reactions, correspond with inflammatory responses following influenza vaccination, as indicated by serum proinflammatory cytokine levels and body temperature. Of note, prior studies show that compared to placebo control, flu vaccine induces greater local reactions (i.e., pain at the

site of injection), but comparable systemic side effects [e.g., 4, 15, 16]. Moreover, reporting of local as well as systemic side effects is influenced by message framing prior to vaccine delivery; those who are presented with more positive messages regarding vaccine benefits and side effects report fewer side effects [6]. Thus, cognitive biases certainly influence symptom reporting. However, despite such effects, the current data support the notion that symptom reporting, at least in some cases, corresponds with biological responses.

From a clinical standpoint, it would be cost prohibitive and lack adequate specificity to assess temperature and baseline inflammatory status in order to identify those who may have less optimal subjective responses to vaccination. In addition, the use of anti-inflammatory medications at the time of vaccination is not advisable to prevent side effects; animal as well as human studies indicate that non-steroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen, tylenol, aspirin, and naproxen, can inhibit antibody production [17–19]. Instead, mild symptoms should be normalized by clinicians. Reassurance should be provided that such symptoms reflect transient responses to the vaccine, rather than influenza, and are not indicative of the immunogenicity of the vaccine. Related to this point, it is notable that in a survey of 2,348 healthcare providers, 47.5% endorsed the belief that, “the influenza vaccination may cause some people to get influenza,” including 22.2% of physicians [3]. As physician recommendation for vaccination is a primary predictor of vaccine uptake, addressing negative beliefs among healthcare personnel is essential to improving vaccination coverage.

This study included only women. Animal models also show that inflammatory responses to flu infection are more severe in females versus males [20]. Moreover, women consistently report more severe local and systemic adverse reactions following receipt of flu vaccine versus men [4, 21–23] and, perhaps relatedly, women are more likely to report negative beliefs about the risks of vaccination compared to men [3, 24]. Thus, generalizability of these findings to men is unknown. In addition, this sample was predominately White and insured, responses may differ in more racially or socioeconomically diverse groups.

As described, in this sample, no significant differences in subjective symptom reporting emerged based on pregnancy status. We have previously reported that in this dataset inflammatory responses following vaccination were highly similar in pregnant and non-pregnant women. However, fear of contracting the flu from the flu vaccine is higher among pregnant women than among the general population, with 43.9% endorsing being “somewhat/very worried about getting sick from this season’s flu vaccine” compared to 29.6% of adults in general [3]. Thus, greater education and reassurance may be needed in this group who is at high risk for influenza-related complications.

In sum, these data demonstrate that subjective symptom reports following vaccination, including pain at the site of injection and, to a lesser extent, systemic symptoms are accompanied by measurable differences in vaccine-induced serum proinflammatory cytokine responses as well as some possible associations with body temperature. Future efforts should aim to identify factors which predispose individuals to greater inflammatory responses to vaccines and to mitigate and/or normalize such effects to improve adherence to vaccine recommendations.

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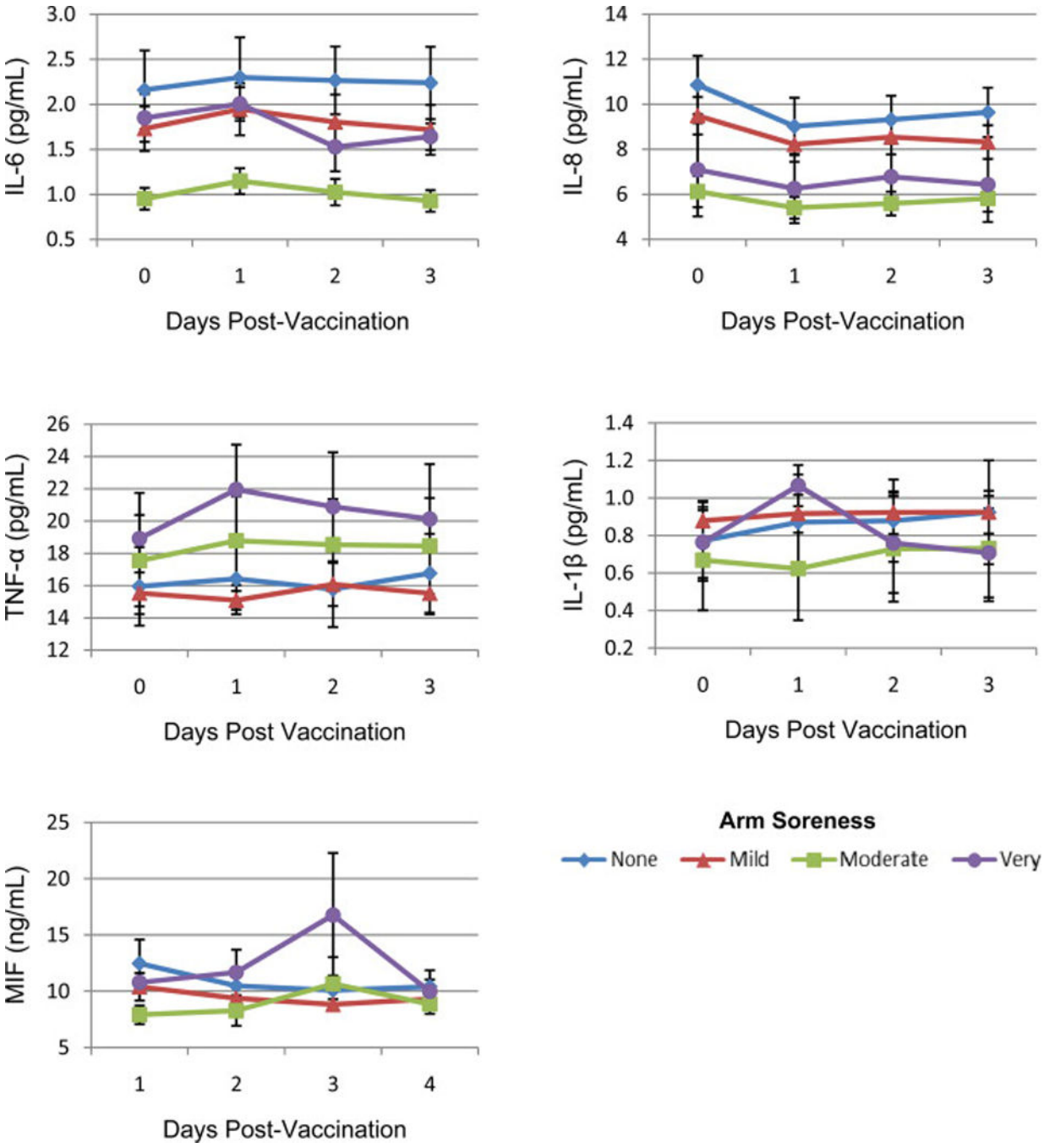


Fig 1. Local reactions following vaccination and serum proinflammatory cytokines

Controlling for baseline, women endorsing very sore local reactions had higher TNF-α at one day post-vaccination than those with mild or no soreness (ps < 0.03) and higher TNF-α at two days post vaccination compared to those with no soreness (p=0.03). Also, controlling for baseline, at two days after vaccination the very sore group had higher MIF than those with mild (p=0.01) or no (p=0.04) soreness and lower IL-6 than those with no soreness (p=0.04).

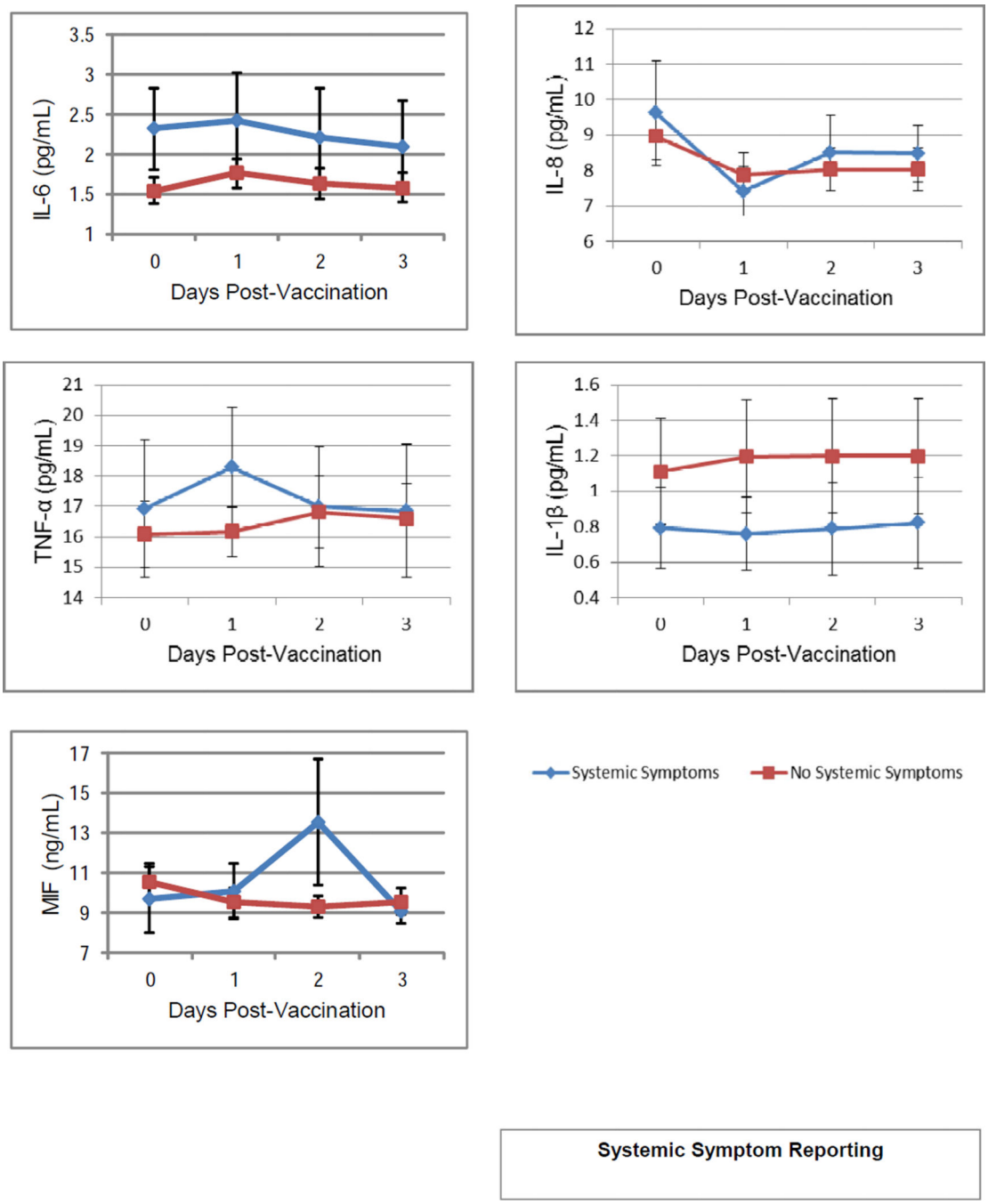
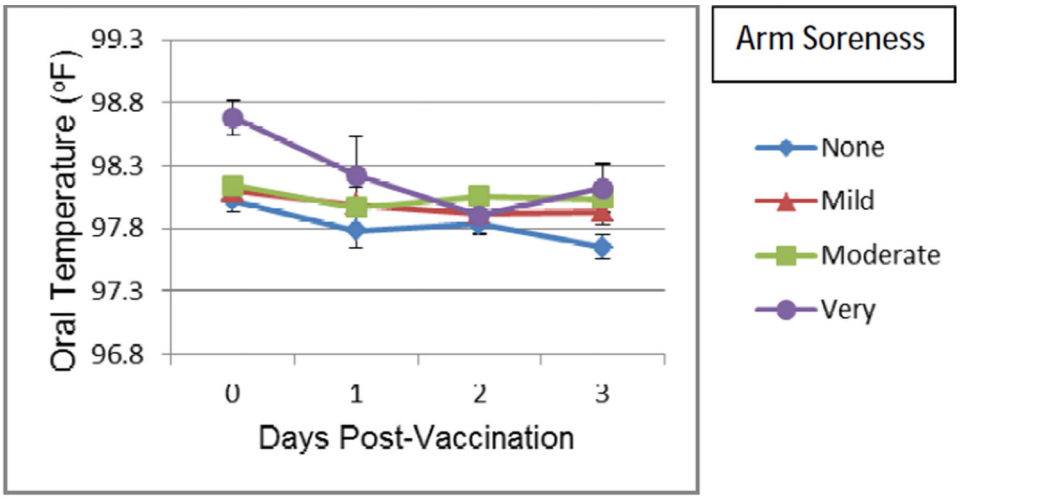
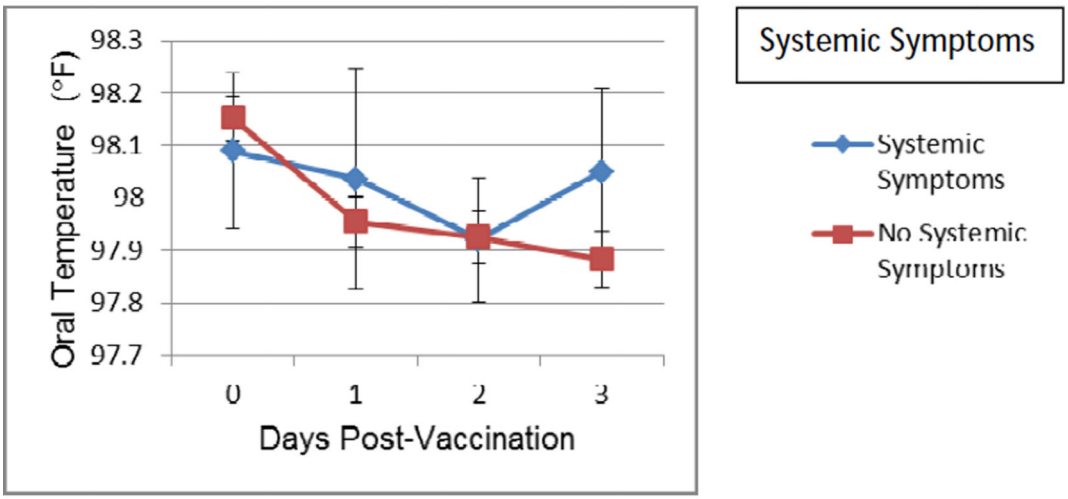


Fig 2. Systemic reactions following vaccination and serum proinflammatory cytokines

Those reporting systemic symptoms had marginally higher serum IL-6 at baseline (p = . 055). In addition, controlling for baseline, those endorsing systemic symptoms exhibited significantly higher serum MIF at two days post-vaccination compared to those without systemic symptoms (p=0.03).



a.



b.

Fig 3.

a. Oral temperature in relation to local symptoms post-vaccination. Very sore responses were related to higher temperatures at baseline compared to moderate, mild, or no soreness (ps < 0.01). In addition, at 3 days post-baseline those with no soreness had lower temperatures than those with mild, moderate, or very sore responses (ps < 0.04).

b. Oral temperature in relation to systemic symptoms post-vaccination. No significant differences were observed at baseline or in response trajectory among those who experienced systemic symptoms versus not.

Table 1

Demographic Characteristics

Age, mean (SD)	29.1 (5.7)
Pregnant	28 (50%)
Race	
African-American	14 (25%)
White	42 (75%)
Ethnicity, Hispanic/Latino	4 (7%)
BMI, mean (SD)	24.9 (5.2)
Marital Status	
Married	31 (55%)
Unmarried, but in a relationship	12 (21%)
Single	13 (23%)
Income	
Less than $30,000	20 (36%)
$30,000 – $74,999	17 (30%)
$75,000 or more	19 (34%)
Education	
High school or less	15 (27%)
Some college	13 (23%)
Bachelor's degree	9 (16%)
Some graduate school or higher	19 (34%)
Smoking	
Current	7 (13%)
Past	14 (25%)
Never	35 (63%)

Table 2

a: Arm Soreness Following Vaccination					
	Not sore	**Mildly sore**	**Moderately sore**	**Very sore**	**Extremely sore**
Day 1	11	31	9	5	0
Day 2	36	16	4	0	0
Day 3	52	3	1	0	0

b: Systemic Symptoms Following Vaccination		
	Absent	**Present**
Day 1	49	7
Day 2	52	3
Day 3	53	2

Other symptoms reported (number of occasions): Headache (n=3); Sleepiness/tired (n=2); Nausea 1 (n=2); Sore throat (n=2); Dizziness (n=1); Mild fever (n=1); Mild achiness (n=1)

Table 3

a: Antibody responses in relation to pain at the injection site			
	Moderately/Very Sore (n=13)	**Mild/No Soreness (n=41)**	**p-value (chi-square test)**
H1N1 Seroconversion	9 (69%)	30 (73%)	0.78
H1N1 Seroprotection	11 (85%)	36 (88%)	0.77
H3N2 Seroconversion	7 (54%)	26 (63%)	0.54
H3N2 Seroprotection	11 (85%)	36 (88%)	0.77
B Seroconversion	6 (46%)	31 (76%)	0.05
B Seroprotection	12 (92%)	40 (98%)	0.38

b: Antibody responses in relation to systemic symptoms			
	Other Symptoms (n=10)	**No Other Symptoms (n=44)**	**p-value (chi-square test)**
H1N1 Seroconversion	7 (70%)	32 (73%)	0.86
H1N1 Seroprotection	8 (80%)	39 (89%)	0.46
H3N2 Seroconversion	6 (60%)	27 (61%)	0.94
H3N2 Seroprotection	9 (90%)	38 (86%)	0.76
B Seroconversion	7 (70%)	30 (68%)	0.91
B Seroprotection	10 (100%)	42 (95%)	1.0[#]

[#]Fishers' Exact Test