

# Adverse Effects and Antibody Titers in Response to the BNT162b2 mRNA COVID-19 Vaccine in a Prospective Study of Healthcare Workers

Si'Ana A. Coggins,<sup>1,2</sup> Eric D. Laing,<sup>1</sup> Cara H. Olsen,<sup>3,4</sup> Emilie Goguet,<sup>1,2</sup> Matthew Moser,<sup>1,2</sup> Belinda M. Jackson-Thompson,<sup>1,2</sup> Emily C. Samuels,<sup>1,2</sup> Simon D. Pollett,<sup>2,4</sup> David R. Tribble,<sup>4,5</sup> Julian Davies,<sup>2,4</sup> Luca Illinik,<sup>2,4</sup> Monique Hollis-Perry,<sup>5</sup> Santina E. Maiolatesi,<sup>2,5</sup> Christopher A. Duplessis,<sup>5</sup> Kathleen F. Ramsey,<sup>5,6</sup> Anatalio E. Reyes,<sup>5,6</sup> Yolanda Alcorta,<sup>5,6</sup> Mimi A. Wong,<sup>5,6</sup> Gregory Wang,<sup>5,6</sup> Orlando Ortega,<sup>2,4</sup> Edward Parmelee,<sup>2,4</sup> Alyssa R. Lindrose,<sup>1,2,5</sup> Andrew L. Snow,<sup>7</sup> Allison M.W. Malloy,<sup>8</sup> Andrew G. Letizia,<sup>9</sup> Daniel Ewing,<sup>9</sup> John H. Powers III,<sup>10</sup> Kevin L. Schully,<sup>11</sup> Timothy H. Burgess,<sup>4</sup> Christopher C. Broder,<sup>1</sup> and Edward Mitre<sup>1,5</sup>

<sup>1</sup>Department of Microbiology and Immunology, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA, <sup>2</sup>Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, Maryland, USA, <sup>3</sup>Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA, <sup>4</sup>Infectious Diseases Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University, Bethesda, Maryland, USA, <sup>5</sup>Clinical Trials Center, Naval Medical Research Center, Silver Spring, Maryland, USA, <sup>6</sup>General Dynamics Information Technology, Falls Church, Virginia, USA, <sup>7</sup>Department of Pharmacology and Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA, <sup>8</sup>Department of Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA, <sup>9</sup>Infectious Disease Directorate, Naval Medical Research Center, Silver Spring, Maryland, USA, <sup>10</sup>Clinical Research Directorate, Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, Maryland, USA, <sup>11</sup>Biological Defense Research Directorate, Naval Medical Research Center-Frederick, Frederick, Maryland, USA

**Background.** The relationship between postvaccination symptoms and strength of antibody responses is unclear. The goal of this study was to determine whether adverse effects caused by vaccination with the Pfizer/BioNTech BNT162b2 vaccine are associated with the magnitude of vaccine-induced antibody levels.

**Methods.** We conducted a single-center, observational cohort study consisting of generally healthy adult participants that were not severely immunocompromised, had no history of coronavirus disease 2019, and were seronegative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein before vaccination. Severity of vaccine-associated symptoms was obtained through participant-completed questionnaires. Testing for immunoglobulin G antibodies against SARS-CoV-2 spike protein and receptor-binding domain was conducted using microsphere-based multiplex immunoassays performed on serum samples collected at monthly visits. Neutralizing antibody titers were determined by microneutralization assays.

**Results.** Two hundred six participants were evaluated (69.4% female, median age 41.5 years old). We found no correlation between vaccine-associated symptom severity scores and vaccine-induced antibody titers 1 month after vaccination. We also observed that (1) postvaccination symptoms were inversely correlated with age and weight and more common in women, (2) systemic symptoms were more frequent after the second vaccination, (3) high symptom scores after first vaccination were predictive of high symptom scores after second vaccination, and (4) older age was associated with lower titers.

**Conclusions.** Lack of postvaccination symptoms after receipt of the BNT162b2 vaccine does not equate to lack of vaccine-induced antibodies 1 month after vaccination.

**Keywords.** adverse effects; antibody titer; COVID-19; mRNA vaccine; SARS-CoV-2.

The implementation of messenger ribonucleic acid (mRNA)-based severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines is playing a major role in efforts to control the SARS-CoV-2 pandemic. Both the Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273 vaccines induce high-titer anti-SARS-CoV-2 antibodies and confer robust protection against morbidity and mortality from SARS-CoV-2 infection [1–4].

One feature of the SARS-CoV-2 mRNA vaccines is the high level of reactogenicity, with both local and systemic reactions reported by the majority of recipients in Phase 1–3 studies [1–4]. A Centers for Disease Control and Prevention vaccine safety monitoring program of adverse effects (AEs) in the US population has found that injection site pain (79.3%), fatigue (53.5%), myalgia (47.2%), headache (43.4%), chills (30.6%), fever (29.2%), and joint pains (23.5%) are frequent after the second dose of the BNT162b2 vaccine [5].

Reactogenicity to vaccines is typically driven by activation of the innate immune system through ligation of pattern-recognition receptors and subsequent release of inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor [6]. Studies suggest type I interferon production elicited by direct mRNA recognition is critical for SARS-CoV-2

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Correspondence: Edward Mitre, MD, Principal Investigator of the Prospective Assessment of SARS-CoV-2 Seroconversion (PASS) Study, Professor, Dept. of Microbiology and Immunology, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814, USA (edward.mitre@usuh.edu).

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control [7–10], and this likely contributes to both immunogenicity and reactogenicity of SARS-CoV-2 mRNA vaccines [6]. Adaptive immune pathways also likely play a role in causing vaccine-mediated symptoms, especially during booster vaccinations or vaccination after infection.

During the rollout of coronavirus disease 2019 (COVID-19) vaccines, it has become commonplace for media outlets and medical professionals to state that presence of symptoms means that a vaccine is “working.” Although this statement is fundamentally true because vaccines “work” by inducing inflammatory responses, it also implies incorrectly that lack of symptoms postvaccination may indicate an absence of appropriate antiviral antibody responses. Notably, there is little data demonstrating correlations between vaccine-induced symptoms and antibody titers with any vaccine platforms [6, 11]. The goal of this study was to assess for correlation between AEs caused by BNT162b2 vaccination and the magnitude of SARS-CoV-2 antibody responses 1 month after second vaccination dose.

## METHODS

### Study Participants

Participants were enrolled in the Prospective Assessment of SARS-CoV-2 (PASS) Study, an observational, longitudinal cohort study of healthcare workers (HCWs) that is evaluating clinical and immunological responses to SARS-CoV-2 infection and vaccination. The cohort consists of generally healthy adults who are ≥18 years old, work at Walter Reed National Military Medical Center, are not severely immunocompromised, and were seronegative for SARS-CoV-2 at time of study enrollment. Details of inclusion and exclusion criteria can be found in the protocol, which has been published [12]. The subset of PASS participants included for analysis in this study

also met the following criteria: (1) no history of COVID-19 diagnosis, (2) seronegative for SARS-CoV-2 antispike protein immunoglobulin (Ig)G before vaccination, (3) received 2 vaccinations with the Pfizer/BioNTech BNT162b2 vaccine, and (4) completed 2 vaccination symptom questionnaires by March 24, 2021 (Supplemental Figure 1). The PASS study was initiated in August of 2020 with study participants seen monthly at the Naval Medical Research Center Clinical Trials Center. The study protocol was approved by the Uniformed Services University Institutional Review Board.

### Ethics Approval and Consent to Participate

This study protocol was approved by the Uniformed Services University of the Health Sciences Institutional Review Board (FWA 00001628; Department of Defense Assurance P60001) in compliance with all applicable Federal regulations governing the protection of human participants. All participants provided written informed consent for participation.

### Assessment of Vaccine-Associated Symptoms

Participants completed a structured vaccine-associated symptoms questionnaire at the first monthly visit after each vaccination dose. Questionnaires asked about the presence and severity of 12 symptoms (8 categorized as systemic, 3 categorized as localized to the vaccine site, and 1 categorized as nonlocal and nonsystemic [see Tables 1 and 2]). Severity of each symptom was defined as symptom intensity and measured on a scale of 0–4 (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = a lot), with scores for each symptom summed for a total symptom severity score of 0–48. The structured questionnaire used for postvaccination adverse effects was based on symptoms queried in published Phase 1 COVID-19 vaccine studies [2, 4]. The severity scale was adopted from that used in

**Table 1. Symptoms Experienced After First Vaccination, Ranked by Frequency**

Symptom	Presence of Symptoms	Symptom Score			
		1	2	3	4
<b>Soreness at injection site<sup>a</sup></b>	188 (91.3)	32 (15.5)	63 (30.6)	66 (32.0)	27 (13.1)
<b>Pain at injection site<sup>a</sup></b>	148 (71.8)	38 (18.4)	44 (21.4)	48 (23.3)	18 (8.7)
<b>Weak or tired<sup>b</sup></b>	87 (42.2)	33 (16.0)	26 (12.6)	23 (11.2)	5 (2.4)
<b>Headache<sup>b</sup></b>	61 (29.6)	22 (10.7)	16 (7.8)	18 (8.7)	5 (2.4)
<b>Body aches or pains<sup>b</sup></b>	58 (28.2)	18 (8.7)	17 (8.3)	15 (7.3)	8 (3.9)
<b>Redness at injection site<sup>a</sup></b>	44 (21.4)	29 (14.1)	11 (5.3)	2 (1.0)	2 (1.0)
<b>Joint pains<sup>b</sup></b>	27 (13.1)	9 (4.4)	8 (3.9)	4 (1.9)	6 (2.9)
<b>Felt nauseous<sup>b</sup></b>	19 (9.2)	10 (4.9)	5 (2.4)	3 (1.5)	1 (0.5)
<b>Felt hot<sup>b</sup></b>	19 (9.2)	7 (3.4)	8 (3.9)	2 (1.0)	2 (1.0)
<b>Felt cold<sup>b</sup></b>	18 (8.7)	6 (2.9)	8 (3.9)	3 (1.5)	1 (0.5)
<b>Chills or shivering<sup>b</sup></b>	17 (8.3)	2 (1.0)	8 (3.9)	5 (2.4)	2 (1.0)
<b>Swollen lymph nodes<sup>c</sup></b>	9 (4.4)	5 (2.4)	3 (1.5)	0 (0)	1 (0.5)

<sup>a</sup>Local symptoms.

<sup>b</sup>Systemic symptoms.

<sup>c</sup>Nonlocal/nonsystemic symptoms.

**Table 2. Symptoms Experienced After Second Vaccination, Ranked by Frequency**

Symptom	Presence of Symptoms	Symptom Score			
		1	2	3	4
<b>Soreness at injection site<sup>a</sup></b>	169 (82.0)	58 (28.2)	54 (26.2)	38 (18.4)	19 (9.2)
<b>Pain at injection site<sup>a</sup></b>	128 (62.1)	54 (26.2)	36 (17.5)	24 (11.7)	14 (6.8)
<b>Weak or tired<sup>b</sup></b>	128 (62.1)	34 (16.5)	32 (15.5)	35 (17.0)	27 (13.1)
<b>Body aches or pains<sup>b</sup></b>	108 (52.4)	15 (7.3)	32 (15.5)	37 (18.0)	24 (11.7)
<b>Headache<sup>b</sup></b>	104 (50.5)	32 (15.5)	32 (15.5)	19 (9.2)	21 (10.2)
<b>Joint pains<sup>b</sup></b>	64 (31.1)	17 (8.3)	16 (7.8)	23 (11.2)	8 (3.9)
<b>Chills or shivering<sup>b</sup></b>	57 (27.7)	9 (4.4)	13 (6.3)	22 (10.7)	13 (6.3)
<b>Felt hot<sup>b</sup></b>	56 (27.2)	20 (9.7)	11 (5.3)	13 (6.3)	12 (5.8)
<b>Felt cold<sup>b</sup></b>	53 (25.7)	13 (6.3)	18 (8.7)	16 (7.8)	6 (2.9)
<b>Redness at injection site<sup>a</sup></b>	39 (18.9)	20 (9.7)	9 (4.4)	7 (3.4)	3 (1.5)
<b>Felt nauseous<sup>b</sup></b>	33 (16.0)	15 (7.3)	9 (4.4)	4 (1.9)	5 (2.4)
<b>Swollen lymph nodes<sup>c</sup></b>	28 (13.6)	8 (3.9)	7 (3.4)	9 (4.4)	4 (1.9)

<sup>a</sup>Local symptoms.<sup>b</sup>Systemic symptoms.<sup>c</sup>Nonlocal/nonsystemic symptoms.

Flu-Pro Plus, a validated patient-reported outcome instrument. Participants were also asked to report the total duration of any vaccine-associated symptoms.

#### Antibody Testing

Immunoglobulin G antibodies against SARS-CoV-2 spike protein and receptor-binding domain (RBD) were measured using microsphere-based multiplex immunoassays (MMIAs) built using Luminex xMAP-based technology as previously described [13] (Supplemental Methods). Our in-house, non-Emergency Use Authorization (EUA) research assay has been tested concurrently with the Mt. Sinai spike/RBD EUA enzyme-linked immunosorbent assay (ELISA), and our thresholds for seropositivity have performed with 99% (334 of 337) concordance for the detection of spike IgG-binding antibodies compared with the Mt. Sinai ELISA [14].

#### Wild-Type Severe Acute Respiratory Syndrome Coronavirus 2 Microneutralization Assays

Neutralizing antibody titers were determined by microneutralization assays as previously described [15].

#### Statistical Analyses

The Wilcoxon signed-rank test was used for paired comparisons and the Mann-Whitney test was used for unpaired comparisons. Kruskal-Wallis or analysis of variance was used when comparing multiple groups. Spearman rank analyses were used to assess for correlations. Spearman partial correlations were used to determine whether age, sex, or weight were independently associated with vaccine-associated symptom scores and to adjust for age, sex, and weight when assessing for correlations between vaccine-related symptom scores and antibody titers. *P* values less than .05 were considered statistically significant.

Analyses were conducted using GraphPad Prism Version 9 and SPSS Version 27. Using the University of California, San Francisco (UCSF) sample size calculator for correlation [16], we calculated that, with a power of 0.8 and an alpha of 0.05, a sample size of 196 participants would enable assessment for correlations with a rho of 0.2. Means are reported as  $\pm$  standard deviation.

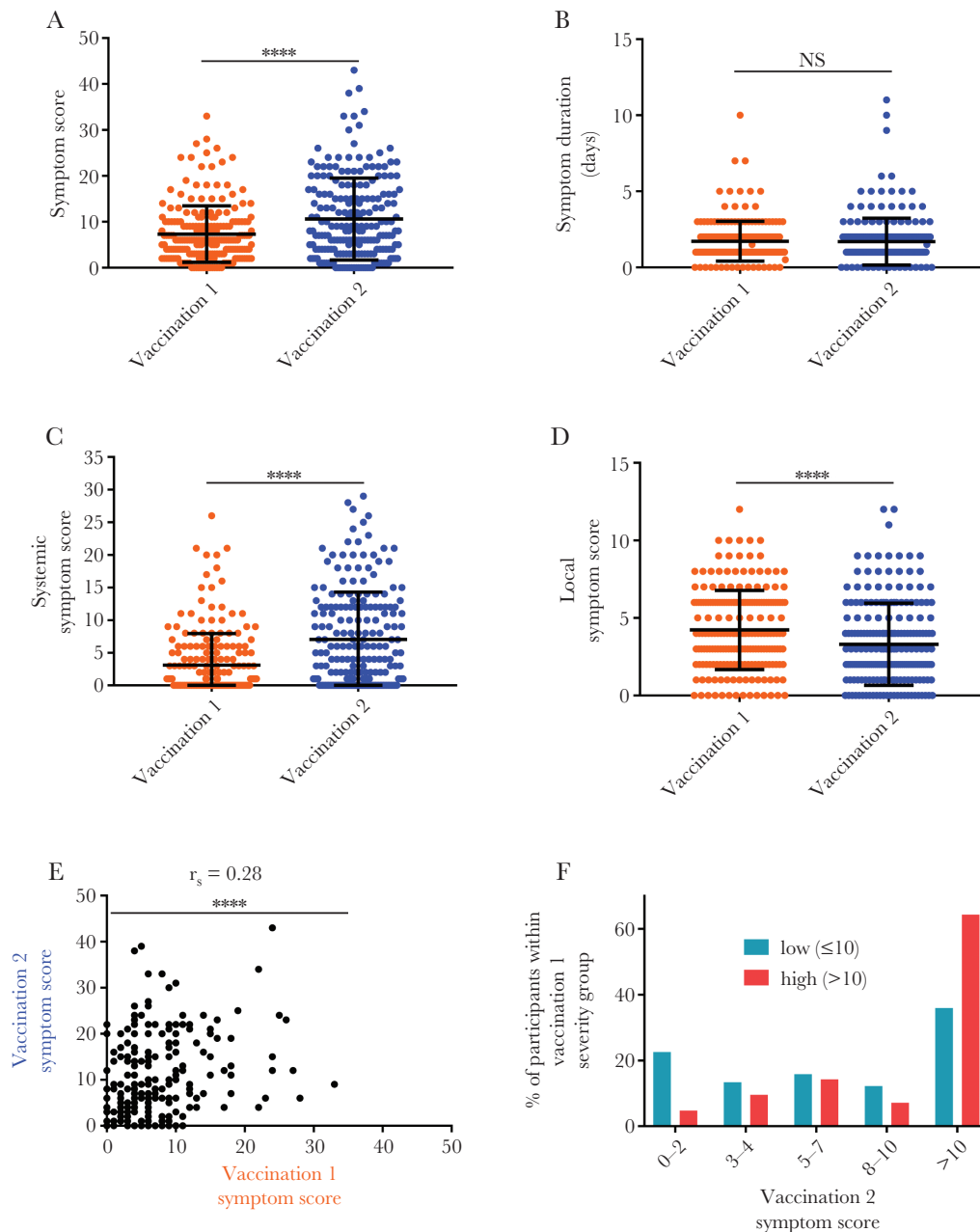
## RESULTS

#### Study Participants Evaluated

A total of 206 participants, of 270 enrolled in the PASS study, were seronegative and without a history of COVID-19 diagnosis when they received the first of 2 BNT162b2 vaccinations, and they provided a serum sample at least 3 weeks after final vaccination. Of these, the median age was 41.5 years old (interquartile range 33–51.25) and 69.4% were female. Antispike antibody levels were quantified by MMIA mean fluorescence intensity (MFI) for all participants and by endpoint dilution titers for the first 101 participants for which serum at least 3 weeks after second vaccination dose was available. Demographic information for the study cohort and titers subgroup is in Supplemental Table 1.

#### Symptom Severity Scores After First and Second Vaccinations

The mean symptom score reported for the second vaccination was significantly greater than that of the first ( $10.6 \pm 8.9$  vs  $7.3 \pm 6.1$ ,  $P < .0001$ ) (Figure 1A), even though there was no significant difference in the duration of symptoms after either vaccination (Figure 1B). To better understand the observed difference in symptom severity, participant symptom scores were subdivided into systemic (maximum score: 32) and local (maximum score: 12) symptom scores. It is interesting



**Figure 1.** Symptom severity after the first vaccination with BNT162b2 correlates with severity of symptoms after the second vaccination. (A) Total symptom severity scores (range 0–48), (B) duration of symptoms, (C) systemic symptom severity scores (range 0–32), and (D) local symptom severity scores (range 0–12) after the first (orange) and second (blue) vaccinations. (E) Correlation of vaccination 1 and vaccination 2 symptom scores. (F) Percentage of subjects categorized as having low ( $\leq 10$ , teal) or high ( $> 10$ , red) total symptom scores after vaccination 1 that exhibited symptom scores of 0–2, 3–4, 5–7, 8–10, or  $> 10$  after vaccination 2.  $N = 206$  for all panels.  $****P < .0001$ . NS = not significant, significance assessed by Wilcoxon signed-rank test for A–D and by Spearman correlation analysis for E. Bars represent mean and standard deviation in A–D.

to note that although the mean systemic symptom score after the second vaccination was significantly greater than after the first (7.0 vs 3.1,  $P < .0001$ ) (Figure 1C), local symptoms displayed an opposing trend with lower severity after the second vaccination (mean 3.3 vs 4.2,  $P < .0001$ ) (Figure 1D). Overall, there was a positive correlation between vaccination 1 and vaccination 2 symptom scores ( $\rho = 0.28$ ,  $P < .0001$ ) (Figure 1E). To determine how frequently individuals with substantial symptoms after the first vaccination develop substantial

symptoms after the second vaccination, participants were separated into 2 groups: a low symptom severity group made up of individuals with vaccination 1 symptom scores less than or equal to 10 ( $n = 164$ , 79.6%) and a high severity group comprising participants with vaccination 1 symptom scores greater than 10 ( $n = 42$ , 20.4%). Approximately 35% of participants in the low symptom severity group reported a symptom score greater than 10 after the second vaccination (Figure 1F). This frequency almost doubled in the high

severity group, with 64% of those participants having recorded a symptom score greater than 10 after the second vaccination (Figure 1F).

### Frequency of Specific Symptoms Experienced After First and Second Vaccine Doses

Soreness at the injection site (vaccination 1: 91.3%, vaccination 2: 82.0%), pain at the injection site (vaccination 1: 71.8%, vaccination 2: 62.1%), and the feeling of being weak or tired (vaccination 1: 42.2%, vaccination 2: 62.1%) were the 3 most common symptoms reported after receiving the first (Table 1) and second (Table 2) doses of the Pfizer-BioNTech BNT162b2 vaccine. Except for the local symptoms of soreness, pain, or redness at the injection site, all symptoms listed on the questionnaire increased in frequency from the first vaccination to the second. For example, although 28.2% of participants experienced body aches or pains after the first vaccination, 52.4% reported this symptom after the second vaccination. This increase was present for even the least common symptom of swollen lymph nodes, which increased from 4.4% to 13.6% of participants after the first and second doses, respectively.

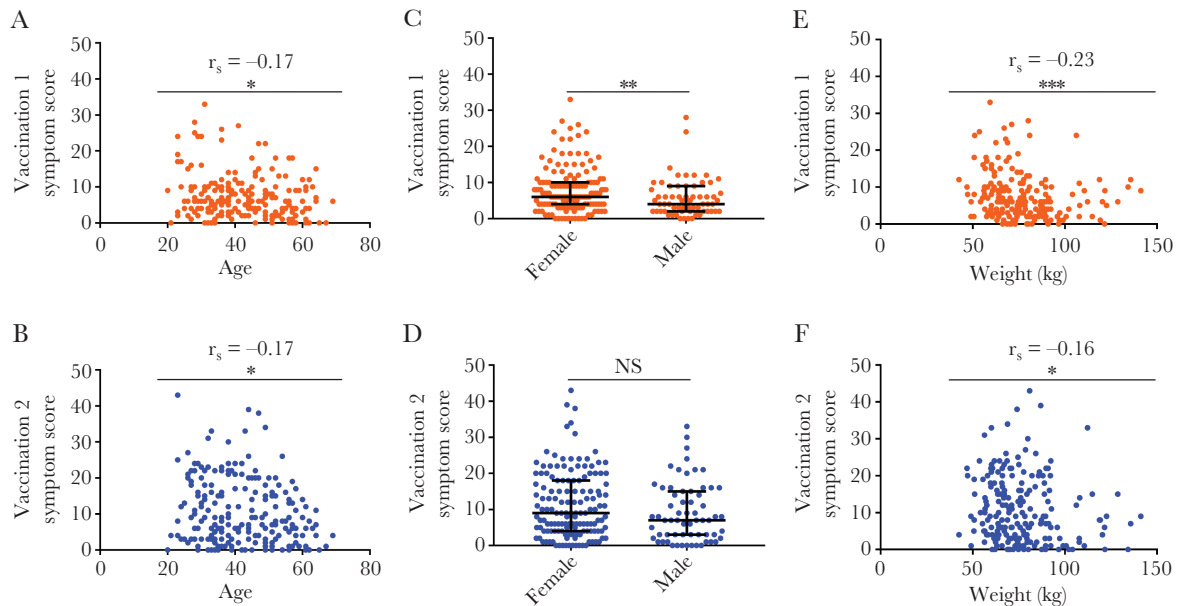
### Relationship Between Vaccine Symptoms, Age, Sex, and Weight

Younger age, female sex, and lower weight were all associated with higher symptom scores when evaluated individually. There was a modest, yet significant, negative correlation between age and symptom severity for both the first ( $r_s = -0.17$ ,  $P = .02$ ) (Figure 2A) and second ( $r_s = -0.17$ ,  $P = .01$ ) (Figure 2B) vaccine doses, representing a 1.7 value decrease in symptom score

for every decade lived (Supplemental Table 2). Female participants reported significantly higher symptom scores than males after the first vaccination (mean  $8.0 \pm 6.4$  vs  $5.7 \pm 5.2$ ,  $P = .006$ ) (Figure 2C). Females also had higher symptom scores after the second vaccination compared to males (mean  $11.3 \pm 9.2$  vs  $9.1 \pm 8.2$ ), but this difference was not statistically significant ( $P = .11$ ) (Figure 2D). Spearman partial correlation analysis determined age to be an independent predictor of total symptom scores after both first (partial  $\rho = -0.17$ ,  $P = .018$ ) and second (partial  $\rho = -0.17$ ,  $P = .018$ ) vaccinations after adjusting for sex and weight (Supplemental Table 2). Although not statistically significant, female sex was consistently found to positively correlate with symptom scores and weight was found to negatively correlate with symptom scores when analyzed with partial Spearman correlations (Supplemental Table 2). No differences in symptom scores based on race for either first or second vaccination were noted (Supplemental Figure 2).

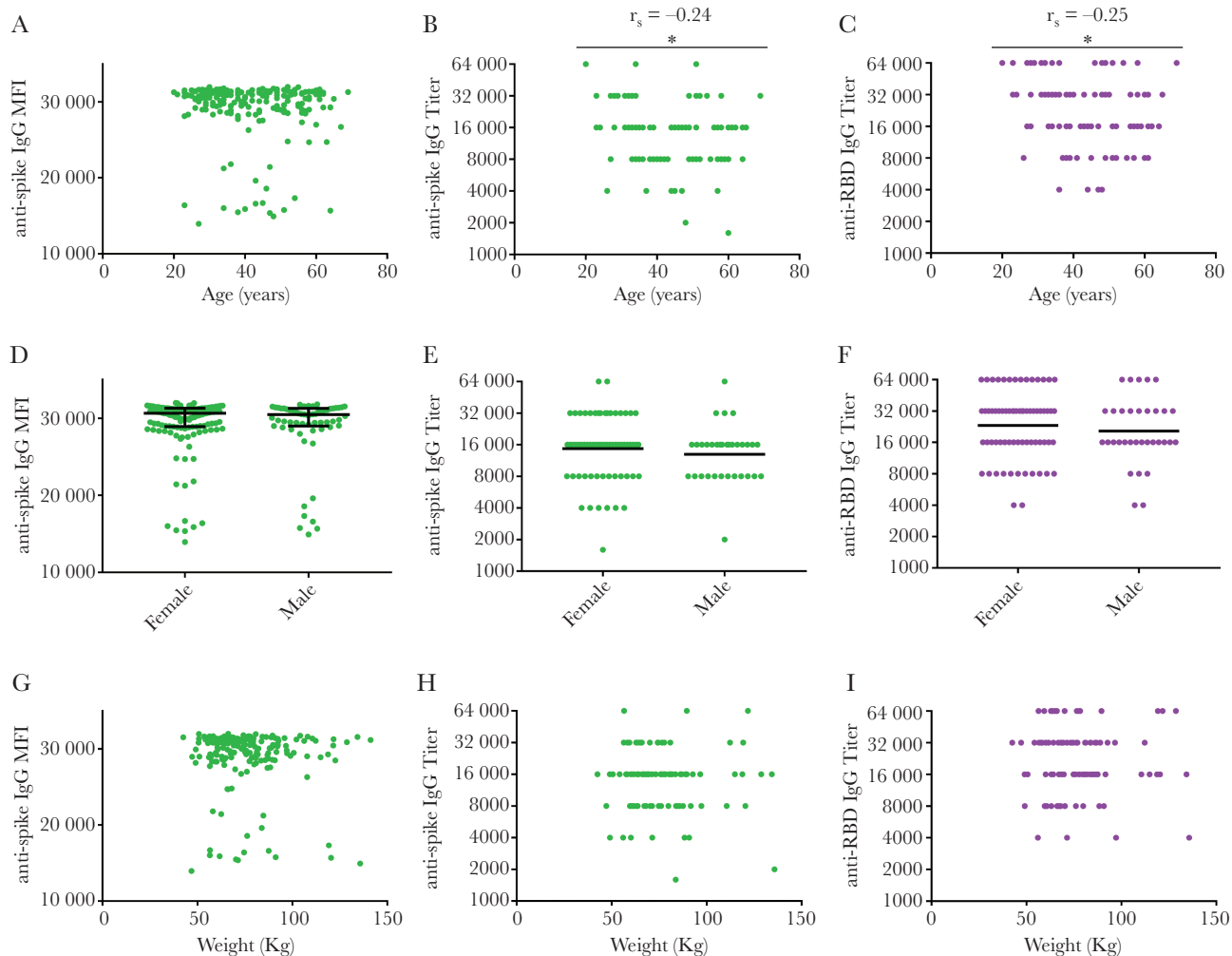
### Lack of Correlation Between Vaccine-Associated Symptoms and Antibody Titers

Time between final vaccination and serum sampling was a mean of  $36.8 \pm 10.0$  days (range 22–104) for the entire cohort and  $33.9 \pm 6.8$  days (range 23–51) for the titers subgroup. Older age, but not sex, weight, or race, was negatively associated with vaccine-induced antibody levels (Figure 3 and Supplemental Figure 3). No correlation between symptom severity after the first or second vaccine doses and IgG reactivity with spike protein was noted (Figure 4A and B). Endpoint dilution assays also exhibited no correlation between vaccine symptom



**Figure 2.** Younger age, female sex, and lower weight are associated with higher symptom severity. Total symptom severity scores after vaccination 1 (orange) and vaccination 2 (blue) graphed against age (A and B), sex (C and D), and weight (E and F). Correlations were assessed by Spearman rank analysis for age and weight. Mann-Whitney analysis was used to assess for significance between males and females.  $N = 206$  for all panels.  $*P < .05$ ;  $**P < .01$ ;  $***P < .001$ . NS is defined as not significant. Bars represent median and interquartile range in C and D.



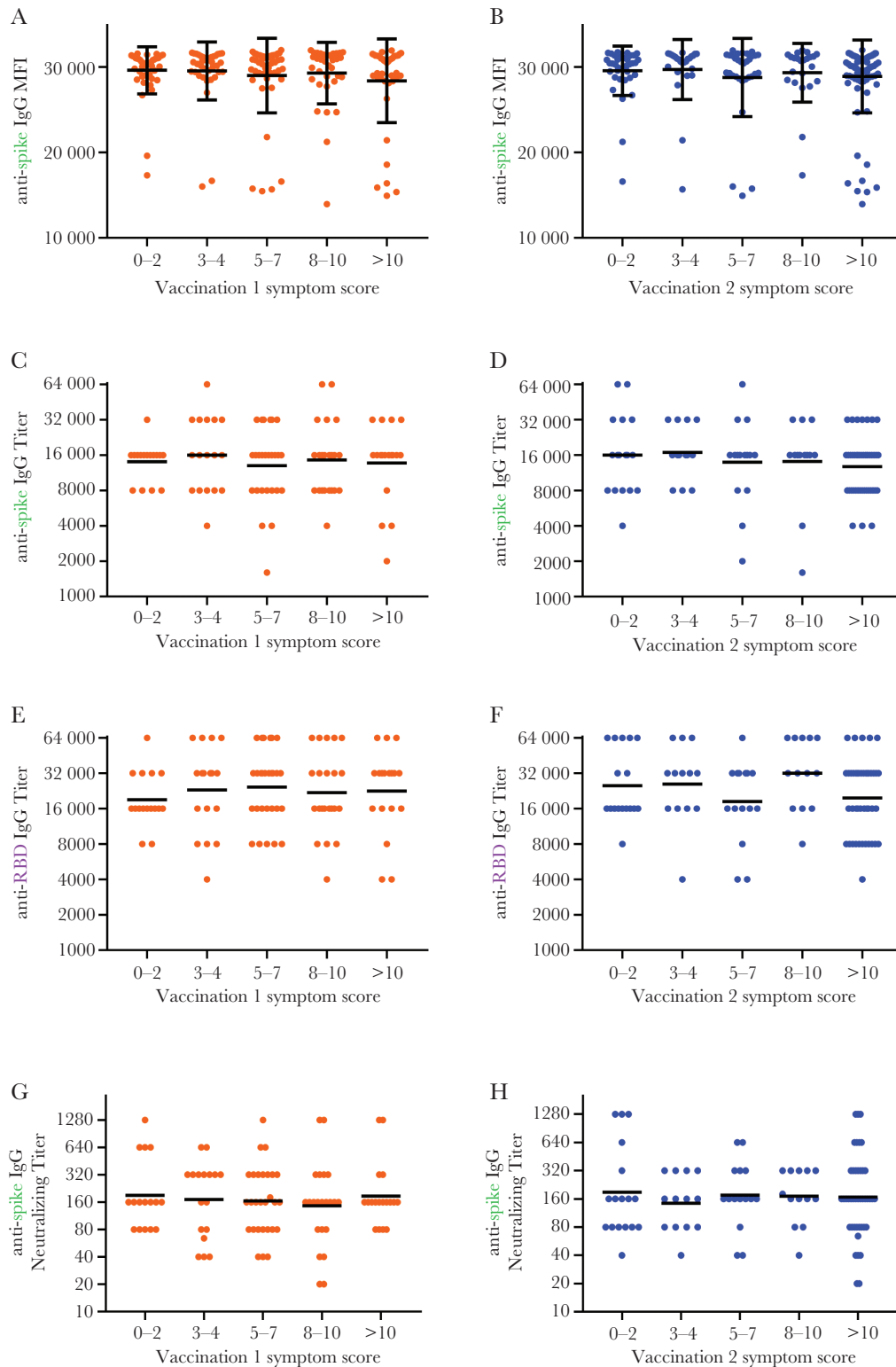


**Figure 3.** Age, but neither sex nor weight, correlates with BNT162b2-induced anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody titers. Samples collected ~1 month after participants received the second vaccine dose were tested for antibodies against SARS-CoV-2 spike protein (green) and receptor-binding domain (RBD) (purple) and plotted against age (A–C), sex (D–F), and weight (G–I). Antibody reactivity against SARS-CoV-2 spike protein in samples diluted 1:400 was assessed in 206 subjects and reported as mean fluorescence intensity (MFI). Endpoint dilution titers were measured in a subset of 101 subjects for both antispike immunoglobulin (Ig) G and anti-RBD IgG. Correlations were assessed by Spearman rank analysis for age and weight, and Mann Whitney analysis was used to assess for significance between males and females.  $N = 206$  for MFI values;  $n = 101$  for antibody titers.  $*P < .05$ . Bars indicate median and interquartile range (D) or geometric mean (E and F). Titers recorded as  $>32000$  are plotted as 64000.

scores and endpoint titers of antispike IgG (Figure 4C and D) or anti-RBD IgG (Figure 4E and F). Lack of correlation was observed with both Spearman rank analyses and with partial Spearman correlations analyses after adjusting for age and sex. In addition, no correlation was observed between vaccine symptoms scores and neutralizing titers (Figure 4G and H). Secondary analyses also revealed no associations between systemic symptoms or lymph node swelling and antispike and anti-RBD titers (data not shown). Analysis of total symptom duration after first or second vaccination revealed no association with antispike MFI levels or anti-RBD IgG titers, although a significant negative correlation was observed with duration of symptoms after second vaccination and antispike IgG titers (Supplemental Figure 4).

## DISCUSSION

Local and systemic symptoms often occur after vaccination and are predominantly due to activation of inflammatory pathways [6]. In this study, we evaluated vaccine-related AEs that occur in response to the Pfizer/BioNTech BNT162b2 mRNA COVID-19 vaccine in a cohort of HCWs. It is notable that we found no correlation between vaccine-related symptom severity and vaccine-induced antibody titers. This lack of correlation was observed even when adjusting for age, weight, and sex. In addition, we observed that (1) symptoms were modestly more common in women and inversely correlated with age and weight, (2) systemic symptoms were more frequent after the second vaccination, (3) high symptom scores after first vaccination were associated with high symptom scores after second



**Figure 4.** Severity of symptoms after vaccination correlates with neither vaccine-induced antispike immunoglobulin (IgG) reactivity nor with titers of antispike and anti-receptor-binding domain (RBD) IgG antibodies. Samples collected ~1 month (mean 36.8 days for A-B and 33.9 days for C-H) after participants received the second vaccine dose of BNT162b2 were tested for antibodies against SARS-CoV-2 spike and RBD proteins using the Luminex microsphere-based multiplex immunoassay. (A and B) Levels of antispike IgG antibodies, as measured by mean fluorescence intensity (MFI), were plotted against symptom scores reported after first (orange) and second (blue) vaccination (N = 206). (C and D) Titers of antispike IgG antibodies, (E and F) anti-RBD IgG antibodies, and (G and H) neutralizing antibodies were plotted against symptom scores reported after first and second vaccination (n = 101). Bars indicate mean and standard deviation (A and B) or geometric mean (C-F). Titers recorded as >32000 are plotted as 64000. Assessments for correlations were conducted by both Kruskal-Wallis analysis with subjects binned into categories of symptom score ranges and by Spearman rank analysis evaluating antibody levels against symptom scores as a continuous variable. All showed no significant correlations.

vaccination, and (4) older age was associated with slightly lower vaccine-induced antibody titers.

We did not observe a significant correlation between vaccine-related AEs and the magnitude of vaccine-induced antibody titers. Individuals with both high and low symptom scores had (1) similar levels of spike-specific IgG antibodies when measured by MFI and (2) similar endpoint dilution titers of spike-specific IgG antibodies, RBD-specific IgG antibodies, and neutralizing antibodies. This lack of correlation was maintained even when controlling for age and sex. Although it would seem logical that vaccine-associated AEs could be predictive of antibody titers, there is little evidence for such a relationship [6]. One study that evaluated different adjuvants for hepatitis B vaccination found a modest association of symptoms after first vaccination with CD4<sup>+</sup> T-cell responses [17]. However, the same study found no association between first vaccination AEs and antibody responses and no associations between symptoms after second vaccination and either CD4<sup>+</sup> T-cell or antibody responses [17]. Consistent with our study, Muller et al [18] did not find an association between symptoms induced by BNT162b2 vaccination and antibody titers.

The lack of correlation between vaccine-associated symptoms and antibody titers has 2 important implications for mRNA SARS-CoV-2 vaccines. First, individuals that exhibit few symptoms after vaccination can be reassured that this does not mean the vaccine “did not work.” Indeed, in this cohort, individuals with few to no symptoms were just as likely to have developed strong antibody responses as individuals that exhibited substantial symptoms. Second, the immunological pathways responsible for mRNA vaccine-induced AEs may not be required for development of robust antibody responses.

The mRNA vaccines induce inflammation through multiple pathways, including ligation of innate immune receptors, release of inflammatory cytokines and chemokines, and activation of antigen-presenting cells, natural killer cells, and antigen-specific T and B cells [19–24]. Given the lack of association between symptoms and antibody titers, we speculate that some pathways may be expendable for development of robust adaptive immune responses. If such pathways can be defined, then efforts on developing mRNA vaccines that minimally activate such pathways could be advantageous.

In regards to vaccination reactogenicity, as with the BNT162b2 clinical trials [3, 4], we observed greater symptom severity after the second vaccination. It is notable that individuals that had a high symptom score after the first vaccination were almost twice as likely to have substantial symptoms after second vaccination compared to those with a low symptom score from the first vaccination. Nevertheless, individuals with few symptoms after the first vaccination still had a 35% chance of having substantial symptoms (total symptom score >10) after second vaccination.

Local symptoms were more frequent than systemic symptoms after both first and second vaccinations, with pain,

soreness, and redness reported in 91%, 72%, and 21% of participants, respectively, after first vaccination and by 82%, 62%, and 19% of participants, respectively, after the second vaccination. These frequencies paralleled those observed in the clinical trials of BNT162b2 [3, 4]. Systemic symptoms were common with symptoms of feeling weak or tired, having body aches or pains, or having joint pains reported by 42%, 28%, and 13% of participants, respectively, after first vaccination and by 62%, 52%, and 31%, respectively, after the second vaccination. Again, these frequencies were similar to clinical trial reports [3].

Partial correlation analysis demonstrated that age was an independent predictor of vaccine-related AEs, with age exhibiting a rho factor of  $-0.17$  for total symptom scores after both vaccine doses in bivariate analyses after controlling for sex and weight. The finding that older age is associated with lower postvaccination symptoms is similar to results of BNT162b2 clinical trials and to findings reported in a comparison study evaluating vaccine responses in individuals greater than 80 years old and less than 60 years old [3, 4, 18].

Although both women and individuals with lower weights were found to have greater vaccine-related symptoms in our study, neither sex nor weight was found to be an independent predictor of symptom scores. Our study may have been insufficiently powered to separate the independent contributions of sex and weight to vaccine-associated symptoms, although sex and weight may simply not be independent predictors. Consistent with our findings, women in a large-scale United Kingdom study were found to have more symptoms than men after BNT162b2 vaccination [25]. In addition, women have been shown to have greater reactogenicity to other vaccines, including measles/mumps/rubella, hepatitis B, influenza, and yellow fever [26, 27]. The determination of whether women and/or low weight individuals have greater BNT162b2 AEs may be informed by additional cohort studies.

The mechanisms by which younger individuals, or women, exhibit greater vaccine-related AEs is unclear, but they may be due to differences in innate immune function. Dendritic cells of older individuals have been shown to release decreased quantities of proinflammatory cytokines when stimulated through pattern recognition receptors [28, 29]. For women, increased AEs may be due to increased responsiveness of innate immune pathways, although differences in anatomy at injection sites, sex hormones, and adaptive immune function may also play a role [30, 31].

Of note, in addition to being associated with lower vaccine-associated symptom scores, age was also found to be significantly correlated with lower titers of vaccine-induced IgG antibodies against spike protein and RBD. Reduced titers were also observed in elderly individuals in both the Phase 1 clinical trial of BNT162b2 and in a recent study evaluating BNT162b2 responses in individuals greater than 80 years old [3, 18]. The mechanisms underlying reduced antibody responses in elderly



individuals are not yet fully elucidated, but they likely include factors such as reductions in T-cell receptor signaling, predilection for naive T cells to differentiate into effector rather than memory T cells, decreased function of follicular helper T cells, and lower antibody production by plasma cells [32].

The present study is limited to antibody responses. It is possible that vaccine reactogenicity, although it does not impact antibody response magnitude, might correlate with vaccine-induced, antigen-specific, T-cell responses. In addition, whether reactogenicity impacts durability of vaccine-induced immune responses will be an important area to explore in future studies. Notably, we did find that symptom duration after second vaccination negatively correlated with vaccine-induced antispikes IgG titers but not with antispikes MFI levels or anti-RBD titers. Although this may reflect a true association, we suspect it is an artifact due to conducting multiple secondary analyses. Another limitation is that the cohort consisted of healthy volunteers without substantial immunocompromising conditions.

## CONCLUSIONS

In conclusion, this study demonstrates that BNT162b2 vaccinations are commonly associated with both local and systemic symptoms. Symptoms are greater after second vaccination, are more common in younger individuals, and do not correlate with vaccine-induced antiviral IgG titers. These findings suggest that patients receiving the BNT162b2 vaccine should be reassured that lack of symptoms does not necessarily equate to lack of desired vaccine function. This study also suggests that it may be possible to design future mRNA vaccines that confer robust antibody responses with lower frequencies of vaccine-associated symptoms. Indeed, emerging studies suggest the balance between vaccine immunogenicity and reactogenicity can be better tuned for COVID-19 mRNA-based vaccines as well [33].

## Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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