mRNA SARS-CoV-2 Immunization Confers Robust Antibody Response in Occupational Healthcare Workers and Fosters Workplace Safety

To the Editor:

Immunization against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a major step in protecting the healthcare worker beyond standard pandemic precautions and infection control measures. Healthcare workers (HCW) are at high risk for SARS-CoV-2 exposure and infection placing burden on the workplace. Hence, reducing SARS-CoV-2 infection of HCWs serves multiple goals in the occupational health arena. These include protecting the health and safety of the HCW as well as reducing transmission of Coronavirus Disease 2019 (COVID-19) in the clinic and the larger workplace it serves. Furthermore, when HCWs demonstrate appropriate pandemic precautions and health practices, they serve as strategic models for other workers. This modeling represents leadership which can inspire optimism and hope in a workforce beleaguered by the pandemic.

Modern medical practices and public health measures (ie, clean water, antibiotics, and vaccination) have transformed public health and human society, and there is good reason to expect that immunizing employees against COVID-19 will similarly transform the workplace burdened by the SARS-CoV-2 pandemic. However, one barrier to this success could be vaccine hesitancy on the part of the HCW as well as the general workforce. Vaccine hesitancy is multidetermined and not amenable to a one-size-fits-all approach. Yet, achieving immunity amongst HCWs is vital for the HCW, the employees they serve, and to communicate confidence and hope for workers whose immunization is pending or in doubt by hesitancy.

With these concerns in mind, we report data from serial immunoassays for anti-SARS-CoV-2 antibodies collected on a group of confirmed COVID-19 naive occupational HCWs who were immunized by mRNA vaccine. Antibody reactivity and kinetics data were compared with results obtained from employees recovered from confirmed COVID-19 from whom serial antibody immunosassays were obtained. In addition, a group of HCW with prior infection by SARS-CoV-2 were immunized and provided preliminary data on antibody formation. Side effect data from immunization of HCWs were also gathered. These results are discussed with respect to level of immune protection attained and how this achievement may mitigate vaccine hesitancy.

METHODS

HCWs (physicians, psychologists, nurse practitioners, nurses, medical technologists, medical assistants, medical administrative assistants, and technicians; N = 62) were immunized with the Pfizer/BioNTech (B162b2; N = 49) or Moderna (mRNA-1273; N = 13) SARS-CoV-2 vaccine. Vaccines were administered by local county health departments following standardized dosing and protocol of the Food and Drug Administration (FDA) Emergency Use Authorization. Serologic immunoglobulin G (IgG) antibody formation was measured at approximate 2-week, 3-week, 4-week, and 5-week intervals post-immunization. Immunosassay was done with the Beckman-Coulter Access SARS-CoV-2 IgG test which detects the receptor binding domain (RBD) spike protein of the SARS-CoV-2 virus. Laboratory analyses were performed in an on-site high-complexity Clinical Laboratory Improvement Amendments (CLIA) lab. A self-report survey (this survey is available in supplemental table 1 (S1), http://links.lww.com/JOM/A889) designed to assess common SARS-CoV-2 vaccine side effects was administered 2 weeks after the boost dose (week 5 for Pfizer/BioNTech; week 6 for Moderna). In addition to reactive versus non-reactive status, signal to cut off ratios (S/CO) for the IgG assays were examined. Statistical analyses were conducted with JMP (Version 15.2.0, SAS Institute Inc., Cary, NC, 1989–2020) and SPSS (Version 26, IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Armonk, NY) software packages.

SARS-CoV-2 infection was diagnosed by results of real time-polymerase chain reaction (RT-PCR) testing using the Applied Biosystems TaqPath COVID-19 Combo Kit. The occupational health clinic has performed over 46,136 RT-PCR tests on employees over an 11-month period on our large workforce of approximately 5700 employees. The testing strategy involved random surveillance of workers in addition to targeted testing of mission-critical employees and testing of symptomatic and exposed workers. As of the time of this report, 684 workers were confirmed positive for COVID-19 (overall new case positivity rate = 1.49%). Recovered confirmed COVID-19 positive employees were offered serial antibody testing. Sera for immunosassay were taken at approximately 14 days and at monthly intervals (30, 60, 90 days, etc) after initial positive RT-PCR result. Recovered COVID-19 employee comparison groups were formed by closely matching mean, median, and range of days since first positive RT-PCR test result with the time intervals at which immunosassay sera were collected on HCWs. Vaccinated HCWs provided self-report ratings of side effect symptoms and perceived global interference in daily activity using a 0 to 4 Likert scale (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = extreme). In addition, 10 HCW who had previously tested positive for SARS-CoV-2 infection were also examined for antibody development. All analyses were conducted as internal quality metrics of existing clinic data; the pertinent Institutional Review Board (IRB) determined that these comparisons did not require full IRB review.

Descriptive statistics for age and sex of the vaccinated HCW and the recovered COVID-19 employees were collected and percent antibody reactive status and the IgG geometric mean at each time interval for the sera samples were determined. Table 1 (T1) summarizes these descriptive statistics. Figure 1 (F1) shows the time trend in antibody...
formation for vaccinated employees and the recovered COVID-19 positive employees.

**Antibody Level Comparisons**

At 2-week comparison, the natural infection group was 79% reactive for IgG antibodies and the pooled Pfizer/BioNTech vaccinated HCWs also were 78% reactive. Percent reactive for the recovered infected and vaccinated groups at 3-, 4-, and 5-week immunoassay were as follows: 95% and 86%, 90% and 100%, and 89% and 100%, respectively. Comparisons of the geometric mean IgG ratios for convalescent employees, Pfizer/BioNTech, Moderna, and pooled vaccinated HCW employees at sample collection intervals evidenced meaningful differences. Previously infected employees showed generally stable and moderate geometric mean IgG levels at and beyond 3 weeks post infection, but Pfizer/BioNTech immunized HCWs demonstrated an approximate 3-fold increase in antibody level at 4 weeks (1 week after

**TABLE 1.** Descriptive Statistics on Recovered COVID-19 and Vaccinated Health Care Worker Employees

|                | Convalescent | Pfizer  | Moderna | Pooled Vaccinated |
|----------------|--------------|---------|---------|-------------------|
| Serum 1        |              |         |         |                   |
| 11–17 days     | N            | 168     | 45      | 57                |
|                | Age (Mean)   | 44.31   | 43.27   | 44.25             |
|                | Age (Std Dev.) | 10.98  | 12.88   | 16.12             |
|                | Male         | 69%     | 24%     | 67%               |
|                | Reactive     | 79.76%  | 77.78%  | 83.33%            |
|                | Draw Day (Mean) | 14.54  | 14.10   | 14.17             |
|                | Geometric S/CO | 3.42   | 3.47    | 7.47              |
|                | N            | 11–17   | 168     |                   |
|                | Age (Mean)   | 45.67   | 46.03   | 45.09             |
|                | Age (Std Dev.) | 11     | 13.79   | 16.63             |
|                | Male         | 71%     | 23%     | 55%               |
|                | Reactive     | 95.24%  | 80.77%  | 100%              |
|                | Draw Day (Mean) | 20.33  | 20.23   | 21.10             |
|                | Geometric S/CO | 4.81   | 4.21    | 11.21             |
|                | N            | 18–23   | 21      |                   |
|                | Age (Mean)   | 45.1    | 46.23   | 45.91             |
|                | Age (Std Dev.) | 11.55  | 13.4    | 15.8              |
|                | Male         | 73%     | 27%     | 73%               |
|                | Reactive     | 90.36%  | 100%    | 100%              |
|                | Draw Day (Mean) | 28.29  | 26.65   | 27.73             |
|                | Geometric S/CO | 5.44   | 5.63    | 6.00              |
|                | N            | 24–29   | 166     |                   |
|                | Age (Mean)   | 46.26   | 46.17   | 45.8              |
|                | Age (Std Dev.) | 11.84  | 13.66   | 16.65             |
|                | Male         | 70%     | 25%     | 70%               |
|                | Reactive     | 89.47%  | 100%    | 100%              |
|                | Draw Day (Mean) | 36.44  | 35.75   | 42.7              |
|                | Geometric S/CO | 3.47   | 38.19   | 39.74             |
|                | N            | 34–44   | 57      |                   |
|                | Age (Mean)   | 46.26   | 46.17   | 45.8              |
|                | Age (Std Dev.) | 11.84  | 13.66   | 16.65             |
|                | Male         | 70%     | 25%     | 70%               |
|                | Reactive     | 89.47%  | 100%    | 100%              |
|                | Draw Day (Mean) | 36.44  | 35.75   | 42.7              |

Total healthcare workers who received vaccinations = 62; total N at each blood draw interval varied. S/CO, signal to cut off ratio, SD, standard deviation.

**FIGURE 1.** Convalescent COVID-19 employees and vaccinated health care worker IgG antibody responses. Mean day of serum 1 = 14 days; serum 2 = 20 days; serum 3 = 28 days; serum 4 = 38 days. IgG, Immunoglobulin G; S/CO, signal to cut off ratio.
boost), and Moderna vaccinated HCWs showed over an approximate 7-fold increase in geometric mean IgG level at 5 weeks (2 weeks after boost). The pooled Pfizer/BioNTech and Moderna geometric mean IgG S/CO ratio for vaccinated HCWs approximately 2 weeks after their respective boosts was almost eight times higher than the natural infection group (38.64 vs 5.44 S/CO). Comparison of the distribution of geometric mean IgG ratios for these collection intervals between recovered COVID-19 employees and vaccinated HCWs showed that the vaccinated groups achieved significantly greater mean IgG levels at week 4 and 5 (after their second [booster] dose) by Wilcoxon Signed-Ranks tests: week 4: $Z = 3.712, P < 0.0002$; week 5: $Z = 6.513, P < 0.0001$. The group geometric means did not differ at the first two sera samplings (week 2: $Z = -0.186, P < 0.853$; week 3: $Z = -0.525, P < 0.594$).

A small group of vaccinated HCWs ($N = 10$) had previously been infected by SARS-CoV-2. Of these eight, had provided serial antibody levels prior to vaccination; 75% were IgG reactive at the first IgG assay (mean of 30 days post infection). The geometric mean IgG S/CO ratios at an average of 30 and 53 days after infection were 2.13 and 2.96. However, 2 weeks after the first vaccination dose (all Pfizer/BioNTech), their geometric mean was 17.90 S/CO, an approximate 6-fold increase. Of note, one HCW’s most recent antibody level (1.61 S/CO) was taken at day 151 from initial infection. At 2 weeks after vaccination, the IgG was 18.5 S/CO, showing a similar strong antibody response to the first vaccination dose.

### Side Effect Analyses

Fifty-three of the 57 HCWs who had received their vaccine boost and complete immunization protocol provided a completed survey (93%). The mean levels of rated interference in daily activity (on a 0 to 4 scale) at dose one and dose two for vaccinated HCWs were 0.23 (SD = 0.69) and 1.34 (SD = 1.43), respectively; this was a statistically significant difference ($t = -4.21, df = 34, P < 0.0001$) showing side effect interference was greater after the vaccine boost. The difference between mean side effect rating at dose one (0.31 [SD = 0.74]) and dose two (0.74 [SD = 0.60]) nearly achieved conventional statistical difference of $P<0.05$ determined by one-way analysis of variance (ANOVA; $df = 23, F = 3.957, P < 0.06$). The two most elevated side effects were pain at injection site (mean dose one = 1.54 [SD = 1.09] and mean dose two = 1.75 [SD = 1.18]) and fatigue (mean dose one = .57 [SD = .96] and mean dose two = 1.58 [SD = 1.34]). The difference between injection site pain level at dose one and two was not significantly significant ($t = 1.24, df = 35, P < 0.22$), but fatigue was rated significantly higher at dose two ($t = -4.79, df = 35, P < 0.000$). Although the mean levels of side effect symptoms and interference in daily activity ratings were generally low, individuals reported a wide range of values. For example, eight persons (20%) reported interference ratings of 3 (severe) or 4 (extreme) after the boost vaccination, 13 persons (37%) reported no interference from experienced side effects, and 3 (9%) persons reported no side effects or interference at all.

### DISCUSSION

These results are important in several ways. First, our data are consistent with early reports from clinical trials and other studies of the two mRNA vaccines for efficacy and with respect to differential antibody response in vaccinated and recovered COVID-19 patients. Although studies have used various antibody assays and characterized different aspects of the humoral immune response, results suggest these mRNA vaccines confer strong immunogenicity. Secondly, measurements of immune response indicators have shown that the second (booster) dose of either Pfizer/BioNTech or Moderna immunization produces robust antibody formation, consistent with our findings of a greater than 7-fold increase in geometric mean IgG level relative to that observed in recovered COVID-19 employees. Of note, our study tracked one indicator of humoral immunity (IgG) using an EUA-approved qualitative assay. However, studies have shown that IgG ratios are very highly correlated with assessments of neutralizing antibodies and other aspects of the adaptive immune response (eg, Spearman rho = 0.95), and the S/CO value of a qualitative immunoassay can be analyzed non-parametrically and examined as a relative indicator for investigative study (as we did). It is important to conduct further studies of vaccine antibody kinetics and durability with different methods and in diverse peoples, with respect to comorbidities and covariates, and their performance relative to SARS-CoV-2 variants. Nonetheless, these early results from mRNA vaccination are very promising.

Third, although individuals report both a range of side effects and severity level (which increase at boost dose), most people experience few, mild, and short-lived side effects. Thus, tolerability of the vaccine appears quite acceptable. Fourth and very importantly, results from prior studies and the current data collectively provide a platform on which increased acceptance of SARS-CoV-2 vaccination can be built. Success begets success. HCWs can capitalize on findings documenting robust antibody response and the low side effect profile of mRNA immunization against SARS-CoV-2. This information may be combined with the strong efficacy data to communicate informed, fact-based, positive, and hopeful messages in the workplace. Empirical evidence provides the information base the HCW may use to discuss SARS-CoV-2 vaccination with hesitant workers, but often information is not sufficient to accomplish behavior change. Surveys show vaccination hesitancy is a significant concern nationally and internationally, a potential barrier to achieving herd immunity, and is not rare within HCWs. A multi-prong approach informed by behavioral science is needed to reduce vaccine hesitancy. Health behavior change addresses fears and knowledge gaps as well as leveraging communication and marketing principles, the power of social modeling, and peer-based example to effect change. These efforts are amplified by empathic listening on the part of the health professional. Actions speak louder than words in inspiring trust, and the HCW seeking to reduce vaccine hesitancy knows the healing relationship itself is curative. Thus, both modeling vaccine acceptance and establishing credibility as an ally of the reluctant individual are important. Effective encouragement proceeds non-judgmentally and makes use of motivational interviewing techniques. In point of fact, a few HCWs in our occupational health clinic were vaccine resistant. Leading by example, providing accessible and fact-based information for knowledge gaps, and relating to the reluctant HCW with interest and a lack of judgment succeeded in increasing our numbers of vaccinated HCWs.

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REFERENCES

1. Honein MA, Christie A, Rose DA, et al. Summary of guidance for public health strategies to address high levels of community transmission of SARS-CoV-2 and related deaths, december 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1860–1867.

2. Koh D. Occupational risks for COVID-19 infection. Occup Med (Lond). 2020;70:3–5.

3. Baker MG, Peckham TK, Seixas NS. Estimating the burden of United States workers exposed to SARS-CoV-2 and related deaths, December 2020. Acad Sci U S A. 2020;111:12283–12287.

4. Plotkin S. History of vaccination.

5. Kwok KO, Li KK, Wei WI, Tang A, Wong SY, Lee SS. Influenza vaccine uptake, COVID-19 vaccination intention and vaccine hesitancy among nurses: a survey. Int J Nurs Stud. 2021;114:103854.

6. Roy B, Kumar V, Venkatesh A. Health care workers’ reluctance to take the Covid-19 vaccine: a consumer-marketing approach to identifying and overcoming hesitancy. NEJM Catal Innov Care Deliv. 2020;1:1–10.

7. Chevallier C, Hacquin AS, Mercier H. COVID-19 vaccine hesitancy: shortening the last mile. Trends Cogn Sci. 2021. S1364-6613(21)00033-4.

8. Walsh EE, French Jr RW, Falsey AR, et al. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. N Engl J Med. 2020;383:2429–2438.

9. Mulligan MJ, Lyke KE, Kitchin N, et al. Phase II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020;586:589–593.

10. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403–416.

11. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med. 2020;383:2427–2438.

12. Widge AT, Rouphael NG, Jackson LA, et al. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. N Engl J Med. 2021;384:880–882.

13. Wang Z, Schmidt F, Weisblum Y, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature. 2021. https://doi.org/10.1038/s41586-021-03324-6.

14. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH 1 T cell responses. Nature. 2020;586:594–599.

15. Issara C, Egger AE, Prokop W, et al. Evaluation of four commercial, fully automated SARS-CoV-2 antibody tests suggests a revision of the Siemens SARS-CoV-2 IgG assay. Clin Chem Lab Med. 2021;54:00010151520210758.

16. Narasimhan M, Mahimainathan L, Raj E, et al. Clinical evaluation of the Abbott Alinity SARS-CoV-2 spike-specific quantitative IgG and IgM assays in infected, recovered, and vaccinated groups. medRxiv. 2021. doi: https://doi.org/10.1101/2021.02.17.21251040.

17. Hunter PR, Brainard JS. Estimating the effectiveness of the Pfizer COVID-19 BNT162b2 vaccine after a single dose. A reanalysis of a study of real-world vaccination outcomes from Israel. MedRxiv. 2021. https://doi.org/10.1101/2021.02.05.21251139.

18. Rossman H, Shilo S, Meir T, Gorfine M, Shalit U, Segal E. Patterns of COVID-19 pandemic dynamics following deployment of a broad national immunization program. medRxiv. 2021. https://doi.org/10.1101/2021.02.08.21251325.

19. Ernsting A, Schwarz R, Lippke S, Schneider M. ‘I do not need a flu shot because I lead a healthy lifestyle’: compensatory health beliefs make vaccination less likely. J Health Psychol. 2013;18:825–836.

20. Paterson P, Maurice F, Stanberry LR, Glismann S, Rosenthal SL, Larson LH. Vaccine hesitancy and healthcare providers. Vaccine. 2016;34:6700–6706.

21. McClure CC, Cataldi JR, O’Leary ST. Vaccine hesitancy: where we are and where we are going. Clin Ther. 2017;39:1550–1562.

22. Szelagyi PG, Thomas K, Shah MD, et al. National trends in the US public’s likelihood of getting a COVID-19 vaccine—April 1 to December 8, 2020. JAMA. 2021;325:396–398.

23. Volpp KG, Loewenstein G, Butenheim AM. Behaviorally informed strategies for a national COVID-19 vaccine promotion program. JAMA. 2021;325:125–126.

24. Goldstein S, MacDonald NE, Guirguis S. Health communication and vaccine hesitancy. Vaccine. 2015;33:4212–4214.

25. Bandura A. Health promotion from the perspective of social cognitive theory. Psychol Health. 1998;13:623–649.

26. Schwarzer R. Modeling health behavior change: How to predict and modify the adoption and maintenance of health behaviors. Appl Psychol. 2008;57:1–29.

27. Webel AR, Okonsky J, Trompeta J, Holzemer WL. A systematic review of the effectiveness of peer-based interventions on health-related behaviors in adults. Am J Public Health. 2010;100:247–253.

28. Olson R, Grosshuesch A, Schmidt S, Gray M, Wippfler B. Observational learning and workplace safety: the effects of viewing the collective behavior of multiple social models on the use of personal protective equipment. J Saf Res. 2009;40:383–387.

29. Pollak KL, Alexander SC, Tulsky JA, et al. Physicians’ empathy and listening: associations with patient satisfaction and autonomy. J Am Board Fam Med. 2011;24:665–672.

30. Frank JD, Frank JB. Persuasion and Healing: A Comparative Study of Psychotherapy. Balti- more, MD: JHU Press; 1993.

31. Hettuera J, Steele J, Miller WR. Motivational interviewing. Annu Rev Clin Psychol. 2005;1:91–111.