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CASE SERIES

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Humoral immune response in healthcare workers after two doses of a BNT162b2 mRNA vaccine in Yucatan, Mexico

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Abstract

The antibody response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as well as the host immune response after vaccination and viral infection have shown to be highly heterogeneous. This is a case series study analysing humoral immune response and vaccination side effects after two doses of a BNT162b2 mRNA among healthcare workers (HCWs) in Mexico. All participants were scheduled for their two doses of mRNA BNT162b2 vaccine and provided information through a questionnaire: demographic characteristics, antibody serum titres and vaccination-related side effects. Blood samples were obtained for serology testing after the first and second doses of vaccine. No serious adverse effects due to vaccination were reported; nonetheless, non-medical HCWs reported more side effects after the second dose. The previous infection with SARS-CoV-2 boosted immune response after receiving the first vaccination (roughly 30 times higher than those without previous infection); nonetheless, after the second dose, the immune response did not show a higher titre as might be expected.

KEYWORDS
COVID-19, humoral immunity, immune response, vaccine

INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly evolved into a global pandemic. Since then, it has affected more than 253 million patients worldwide, causing more than 4 million deaths.[1] In Mexico, coronavirus disease 2019 (COVID-19) has shown a three times higher case fatality rate (8%–10%) compared to countries with better access to health resources and this rate is representative among elderly patients.[2]

The clinical presentation of SARS-CoV-2 infection is highly variable, ranging from asymptomatic or subclinical infection to severe or critical illness with higher mortality rates, especially in patients with a history of one or more morbidities, including obesity and type 2 diabetes mellitus.[3] Mexico has a higher prevalence of non-communicable diseases, which are being independently associated with adverse outcomes.[4]

Although there are multiple reports of humoral behaviour after the application of two doses of vaccine, these reports derive from non-Latino populations with several factors differing from our population. Therefore, it is imperative to increase our knowledge of the immune response generated after the administration of two doses of COVID-19 vaccine considering ethnicity. So far, it has been reported that the antibody response can be very heterogeneous, and the clinical value of antibody testing depends largely on our understanding of host immune responses during viral infection.[5,6] The duration of antibody responses against SARS-CoV-2, both in convalescent and in vaccinated subjects, is one of the main research topics, since the duration of protection can be at least partially due to humoral immunity.[7] Low or undetectable antibody titres in some patients underscore the need to evaluate the role of the humoral

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immune response. Because COVID-19 is a new disease, the kinetics of the antibody response are not fully understood.[8]

This study describes the dynamics of IgG antibody titres against the SARS-CoV-2 spike surface protein in serial blood samples collected from 79 Mexican healthcare workers (HCWs) vaccinated with BNT162b2, BioNTech—Pfizer. The clinical value of antibody testing is also discussed.

METHODS

Study subjects

This is a cohort study conducted at the High Specialty Regional Hospital of Yucatan Peninsula in Mexico. Seventy-nine HCWs over 18 years of age with and without previous COVID-19 (17 previously confirmed with reverse transcription-polymerase chain reaction [RT-PCR] for SARS-CoV-2 and 62 without infection) were included. Subjects were scheduled for their first (13–15 January 2021) and second (18–20 February 2021) doses of 0.3 ml of mRNA vaccine (30 μg, BNT162b2 developed by BioNTech and Pfizer). This study was approved as part of the COVID-19 research programme by the Institutional Review Board (Ethics Committee) of the High Specialty Regional Hospital of Yucatan Peninsula in Mexico (Protocol number 2020-023).

Procedures

All subjects filled out a questionnaire using an electronic platform and provided the following data: demographic characteristics (age [based on date of birth], weight, height, body mass index [BMI]), medical history of morbidities (diabetes [yes/no], hypertension [yes/no], asthma [yes/no], hypothyroidism [yes/no], immunological diseases [yes/no], tobacco use [yes/no], overweight/obesity [yes/no]), previous COVID-19 diagnosis (yes/no) based on RT-PCR result and date of first and second dose of BNT162b2 vaccine, as well as adverse effects related to the first and second applications of the vaccine (pain [yes/no], fever [yes/no], diarrhoea [yes/no], headache [yes/no], abdominal pain [yes/no], myalgias and/or arthralgias [yes/no], fatigue [yes/no]), date of the determination of serum antibodies against the SARS-CoV-2 spike protein (anti-S1/S2) and antibody titres (AU/ml). All participants signed an informed consent form, which was sent by e-mail using the Survey Monkey™ platform.

Blood samples were obtained from participants for serology testing 35 days (interquartile range [IQR] 35–35) after the first and 28 days (IQR 28–29) after the second doses of vaccine administration. They were tested for antibodies against SARS-CoV-2 spike protein (anti-S) using the LIAISON® SARS-CoV-2 S1/S2 IgG kit (DiaSorin), and the results were expressed as arbitrary units per ml (AU/ml). The baseline results were classified as positive or negative according to the reference value determined by the manufacturer (positive, higher than 14.5 AU/ml).

The information obtained from the surveys and the antibody titres of each participant were collected in a general database for primary analysis.

Statistical analysis

GraphPad version 9 (GraphPad Software) was used for statistical analyses and generation of dot plots. Variables of data were considered non-normally distributed and are reported as medians and IQR (Q1–Q3) and frequencies with

TABLE 1 Overall characteristics of the study population

Variable	Subjects, $n = 79$
Age (years)	42 (35–46)
Male sex	28 (35.4%)
BMI (kg/m^2)	27.5 ± 4.9
BMI ≥ 30 kg/m^2	21 (26.5%)
HCW's position	
Non-medical (administrative workers)	6 (7.5%)
Medical (nurse, physician)	73 (92.5%)
Any morbidity	39 (49.4%)
Obesity	21 (26.5%)
Hypertension	8 (10%)
Hypothyroidism	4 (5%)
Heart disease	0 (0%)
Asthma	6 (7.5%)
Current or former smoker	0 (0%)
Immunological disease	0 (0%)
Previous SARS-CoV-2 exposure	17 (21.5%)
Spike IgG titres (UA/ml)—first dose	85 (60–153)
Side effects—first dose	68 (86%)
Pain	58 (73.5%)
Headache	23 (29%)
Diarrhoea	4 (5%)
Abdominal pain	5 (6%)
Fever	7 (9%)
Myalgias/arthralgias	16 (20%)
Fatigue	28 (35.5%)
Spike IgG titres (UA/ml)—second dose	359 (284–1400)
Side effects—second dose	64 (81%)
Pain	58 (73.5%)
Headache	24 (30.5%)
Diarrhoea	3 (4%)
Abdominal pain	4 (5%)
Fever	8 (10%)
Myalgias/arthralgias	20 (25.5%)
Fatigue	33 (42%)

Abbreviations: BMI, body mass index; HCW, healthcare worker; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UA, arbitrary units.

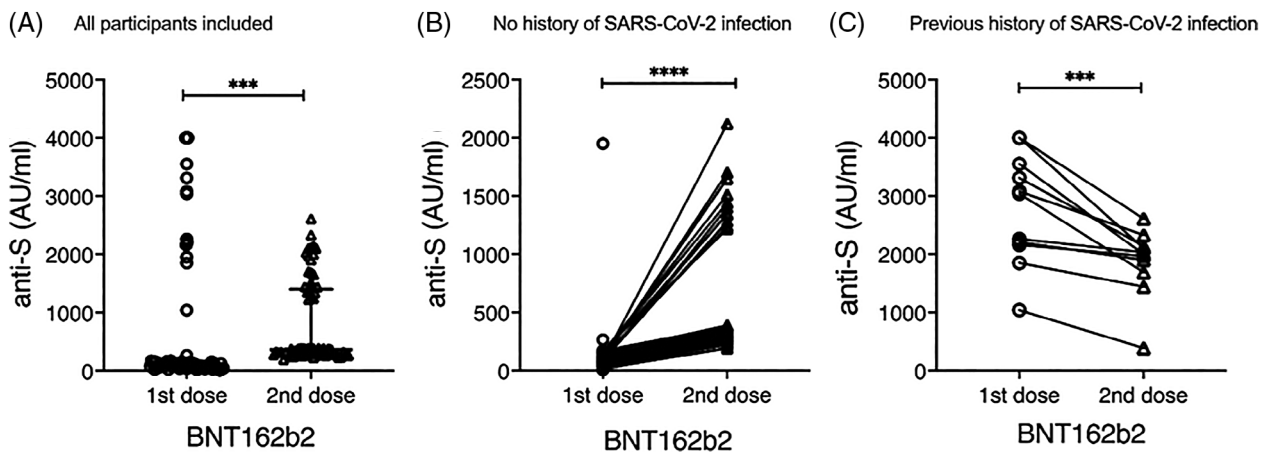

FIGURE 1 Assessment of total antibody response after the first and second doses of Pfizer-BNT162b2 vaccine in the entire population (A). Antibody titres in participants without a previous history of SARS-CoV-2 infection (B). Antibody titres in participants with a previous history of SARS-CoV-2 infection (C). Comparisons were performed with the Wilcoxon signed-rank test; ***$p < 0.001$, ****$p < 0.0001$

percentages. Between-group comparisons (sex [male vs. female], BMI [≥30 vs. <30 kg/m^2], HCW's position [non-medical vs. medical], morbidity [no vs. yes] and previous COVID-19 [no vs. yes]) were performed using Wilcoxon signed-rank test for continuous variables and Fisher's exact test for categorical variables. A p-value of <5% was considered statistically significant.

RESULTS

Demographic characteristics

Seventy-nine enrolled subjects received their vaccination between 13–21 January 2021 (first dose) and 15–17 February 2021 (second dose).

The median age of the participants was 42 years (IQR 35–46) and 35% were male. Five out of 10 HCWs reported at least one morbidity; of these, the most frequent was obesity (25%). Other demographic characteristics are described in Table 1.

Spike IgG antibodies titres overall analysis stratified by groups

Geometric mean titres of IgG antibodies to SARS-CoV-2 spike protein (S1/S2) increased after the first vaccination. However, after stratification by groups, the titres of subjects previously infected were approximately 30 times higher (2210 AU/ml, IQR 1040–3310) than those vaccinated without prior exposure to SARS-CoV-2 (75 AU/ml, IQR 52–107) after one vaccine dose and six times higher at the same time points after the second vaccine dose (1935 AU/ml [IQR 386–2100] vs. 328 AU/ml [IQR 279–386], $p < 0.001$] (Figure 1A, Table 2).

When antibody titres were analysed, two different patterns of humoral responses were observed. Most individuals ($n = 59$) showed a significant increase in antibody titres after the second dose of vaccine ($p < 0.0001$) (Figure 1B); however, we observed a small number of participants ($n = 12$) in whom the antibody response decreased ($p = 0.0005$) (Figure 1C). This group of individuals with decreased humoral immune responses were older than 50 years and had a prior history of SARS-CoV-2 infection in common.

Vaccine-reported overall side effects stratified by groups

About eight out of 10 HCWs reported an adverse effect with the administration of the vaccine, regardless of whether it was the first or second dose; however, none was classified as a severe side effect. After stratification by sex, BMI, HCW's position, morbidity and previous COVID-19, we observed different patterns of response (Table 2). After the administration of the first dose, fever (19% vs. 5%, $p = 0.076$) was more frequent in those with a BMI ≥ 30 kg/m^2. Among HCW's subgroups, medical HCWs reported pain during inoculation (33% vs. 77%, $p = 0.04$), whereas non-medical HCWs have more headache (67% vs. 26%, $p = 0.056$). After the second dose, fatigue was more prevalent in females (51% vs. 28.5%, $p = 0.062$), and there was a significant increase in the prevalence of headache after the second dose compared to their first vaccination among non-Medical HCWs (83% vs 33%); also, compared to the medical HCWs, non-Medical HCWs have a higher prevalence of headache, diarrhoea, abdominal pain and fatigue (Table 2). Finally, myalgias/arthralgias were more frequent in HCWs without morbidities (41% vs. 10%, $p = 0.004$).

TABLE 2 Spike IgG antibodies titres and vaccination side effects stratified by sex, BMI, HCW's position and previous exposure to SARS-CoV-2

Variable	Sex		BMI		HCW's position		Previous COVID-19	
	Female ($n = 51$)	Male ($n = 28$)	<30 kg/m^2 ($n = 58$)	≥30 kg/m^2 ($n = 21$)	Non-medical ($n = 6$)	Medical ($n = 73$)	No ($n = 62$)	Yes ($n = 17$)
Age (years)	42 (37–47)	41 (35–43)	42 (35–46)	42 (38–45)	41 (33–52)	42 (37–46)	42 (38–46)	37 (34–42)
Spike IgG titres (UA/ml)—first dose	89 (61–150)	76 (47–1010)	76 (59–150)	101 (67–153)	91 (84–99)	83 (59–153)	75 (52–107)	2210 (1040–3310)[†]
Spike IgG titres (UA/ml)—second dose	338 (282–1345)	382 (293–1650)	343 (280–1440)	367 (317–1375)	1700 (1350–1970)[§]	348 (284–1280)	328 (279–386)	1935 (386–2100)[†]
Side effects—first dose								
Pain	37 (72.5%)	21 (75%)	41 (71%)	17 (81%)	2 (33%)	56 (77%)[‡]	45 (73%)	13 (76.5%)
Headache	17 (33%)	6 (21%)	17 (29%)	6 (28.5%)	4 (67%)[‖]	19 (26%)	15 (24%)	8 (47%)[¶]
Diarrhoea	3 (6%)	1 (3.5%)	2 (3.5%)	2 (9.5%)	0 (0%)	4 (5.5%)	4 (6.5%)	0 (0%)
Abdominal pain	4 (8%)	1 (3.5%)	3 (5%)	2 (9.5%)	0 (0%)	5 (7%)	5 (8%)	0 (0%)
Fever	3 (6%)	4 (14%)	3 (5%)	4 (19%)[^]	0 (0%)	7 (9.5%)	7 (11%)	0 (0%)
Myalgias/arthralgias	11 (21.5%)	5 (18%)	11 (19%)	5 (24%)	2 (33%)	14 (19%)	12 (19%)	4 (23.5%)
Fatigue	20 (39%)	8 (28.5%)	21 (36%)	7 (33%)	4 (67%)	24 (33%)	20 (32%)	8 (47%)
Side effects—second dose								
Pain	37 (74%)	21 (75%)	42 (74%)	16 (76%)	5 (83%)	53 (74%)	45 (73%)	13 (76.5%)
Headache	17 (34%)	7 (25%)	20 (35%)	4 (19%)	5 (83%)[Δ]	19 (26%)	18 (29.5%)	6 (35%)
Diarrhoea	3 (6%)	0 (0%)	3 (5%)	0 (0%)	2 (33%)[∫]	1 (1.5%)	3 (5%)	0 (0%)
Abdominal pain	4 (8%)	0 (0%)	4 (7%)	0 (0%)	2 (33%)[∞]	2 (3%)	4 (6.5%)	0 (0%)
Fever	7 (14%)	1 (3.5%)	5 (9%)	3 (14%)	2 (33%)	6 (8%)	6 (10%)	2 (11.5%)
Myalgias/arthralgias	13 (26%)	7 (25%)	16 (28%)	4 (19%)	3 (50%)	17 (24%)	16 (26%)	4 (23.5%)
Fatigue	25 (51%)[*]	8 (28.5%)	25 (44%)	8 (40%)	6 (100%)[Ω]	27 (38%)	26 (43.5%)	7 (41%)

Note: Between-group comparisons were performed as follows: Wilcoxon's rank sum test for continuous variables and Fisher's exact test for categorical variables. Sex: $^{*}p = 0.062$. BMI: $^{\wedge}p = 0.076$. HCW's position: $^{\S}p = 0.064$; $^{\ddagger}p = 0.04$; $^{\|}p = 0.056$; $^{\Delta}p = 0.009$; $^{\int}p = 0.014$; $^{\infty}p = 0.029$; $^{\Omega}p = 0.005$. Previous COVID-19: $^{\dagger}p < 0.001$; $^{\P}p = 0.078$.

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; HCW, healthcare worker; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UA, arbitrary units.

DISCUSSION

Vaccine-induced population immunity is a critical global strategy to control COVID-19. Vaccination programmes should maximize early impact; particularly with the accelerated spread of new variants, optimal timing of booster doses for vaccinated populations with risk factors should be considered.[9]

Among subjects with previous SARS-CoV-2 infection, vaccination increased IgG antibody titres against the SARS-CoV-2 spike protein (anti-S1/S2) by a 30-fold higher than their peers with no previous history of COVID-19 after the administration of the first dose of vaccine. This response has been observed in HCWs with a history of previous SARS-CoV-2 infection immunized in other countries.[10] Our findings add evidence of a consistent response after the first dose of vaccine among subjects of different ethnic origins, now reflected in the Latino population of Mexico. The rapid and robust antibody response (booster effect) to vaccination in subjects with previous exposure to SARS-CoV-2 (immune priming) confirms the persistence of immune memory currently proposed as vigorous hybrid immunity (priming and vaccination-derived immunity).[11] Adverse effects after the administration of the first dose of the vaccine were more frequent in previously infected female HCWs in contrast to what has been described in the results of the phase 3 trial of the BNT162b2 mRNA vaccine.[12] Adverse effects that develop after vaccination have received little attention from the authors, as the specific cause of their development is poorly described. Sprent and King have analysed that most of the symptoms can probably be attributed simply to the exuberant production of a cytokine that plays a vital role in potentiating the early stages of the immune response (interferon type IFN-I).[13]

With the evidence that vaccine has ultimately shown to reduce the medium-term risk of severe disease, current vaccine supplies could save more lives if used in previously unvaccinated populations than if used as boosters in vaccinated populations.[14]

The reduction in antibody titres observed in our small group of patients with a history of SARS-CoV-2 infection and older than 50 years could be due in part to the loss of antibodies generated in response to infection, leaving only those resulting from vaccination. The clinical implications of this finding are unknown and long-term studies are needed to identify and clarify the possible risk factors. Based on our results, hypotheses about the prioritization for a third dose of vaccination might be strengthened in individuals without previous infection or over 50 years of age who have a higher risk of severe COVID-19 and a lower humoral response.

Finally, among Mexican population, it is well known that the great problem derived from obesity and HCWs are not exempt because we documented a frequency of 25%; these data are in line with reports derived from the United States where 14.3% of vaccinated HCWs were identified with obesity.[15]

Our study has some limitations. The main limitation is the small number of subjects included with and without a history of previous SARS-CoV-2 infection, which may allow us to look for associations between variables or to establish causal relationships. Also, we were not able to measure neutralizing antibodies as we do not have access to such technology. Nonetheless, this is the first report describing the dynamics of the humoral immune response in our population.

In conclusion, this study provides some evidence on the dynamics of the antibody response among HCWs vaccinated against SARS-CoV-2 and shows the relevance of vaccination schedules in individuals older than 50 years or with increased risk factors. It also provides an insight regarding side effects after either first or second doses of vaccination and reinforces the recent recommendations issued by the CDC regarding the third booster dose in individuals highly exposed or susceptible by age or morbidities to develop severe COVID-19.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article and/or its supplementary material files. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

This study was approved as part of the COVID-19 research programme by the Institutional Review Board (Ethics Committee) of the High Specialty Regional Hospital of Yucatan Peninsula in Mexico (protocol number 2020-023).

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