Short communication

BNT162b2 mRNA COVID-19 vaccine Reactogenicity: The key role of immunity

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ABSTRACT

We examined the impact of pre-existing SARS-CoV-2-specific cellular immunity on BNT162b2 mRNA COVID-19 vaccine reactogenicity. Of 96 healthcare workers (HCWs), 76% reported any vaccine reaction (first dose: 70%, second dose: 67%), none of which was severe. Following first dose, systemic reactions were significantly more frequent among HCWs with past infection than in infection-naïve individuals, and among HCWs with pre-existing cellular immunity than in those without it. The rate of systemic reactions after second dose was 1.7 and 2.0-times higher than after first dose among infection-naïve HCWs and those without pre-existing cellular immunity, respectively. Levels of SARS-CoV-2-specific T-cells before vaccination were higher in HCWs with systemic reactions after the first dose than in those without them. BNT162b2 vaccine reactogenicity after first dose is attributable to pre-existing cellular immunity elicited by prior COVID-19 or cross-reactivity. Reactogenicity following second dose suggests an immunity-boosting effect. Overall, these data may reduce negative attitudes towards COVID-19 vaccines.
Study Registration.
The study was registered on clinicaltrials.gov, NCT04402827.

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1. Introduction

The BNT162b2 (Pfizer-BioNTech) mRNA coronavirus disease 2019 (COVID-19) vaccine showed to be highly effective in preventing COVID-19 in phase 3 clinical trials [1], and able to elicit robust humoral and cellular responses against SARS-CoV-2 [2]. From a safety standpoint, reactogenicity, defined as inflammatory events that occur soon after vaccination, was reported in up to 83% of previously uninfected individuals [1,3]. Real-life studies observed variable rates of vaccine-induced reactions mostly after the second dose [4,5], although the mechanisms underlying BNT162b2 mRNA COVID-19 vaccine reactogenicity are still poorly understood.

Cellular responses against SARS-CoV-2 epitopes are observed in almost all individuals after recovery from COVID-19, even in those with asymptomatic infection [6], or undetectable SARS-CoV-2-specific IgG [7]. Additionally, cellular responses were described in 40–60% of unexposed individuals, suggestive of cross-reactive immunity to endemic human coronaviruses [8,9]. Hypothetically, cellular immunity against SARS-CoV-2 could be related to the emergence of vaccine reactogenicity. Therefore, we aimed to evaluate BNT162b2 mRNA COVID-19 vaccine reactogenicity in healthcare workers (HCWs) with past SARS-CoV-2 infection or preexisting T-cell immunity to SARS-CoV-2 peptides.

2. Methods

The COVEX-2 study is an observational prospective cohort study that assessed the immune response and incidence of SARS-CoV-2 infection among HCWs at a tertiary university hospital. One hundred and twenty-six HCWs underwent blood test from May to October 2020 to evaluate humoral and T-cell responses to SARS-CoV-2 and completed a questionnaire about age, sex, body

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Table 1
Baseline clinical characteristics and laboratory findings of the study population.

	All groups (n = 96)	HCWs with past SARS-CoV-2 infection (n = 42)	Infection- naïve HCWs (n = 54)	p-value
Age [years], mean (range)	44 (26–65)	43 (26–63)	46 (30–65)	0.240
Gender				
Female	63 (66)	24 (57)	39 (72)	0.120
Male	33 (34)	18 (43)	15 (28)	
Body mass index [kg/m^2]	23.5 (21.5–26.7)	23.4 (21.6–24.6)	23.7 (21.4–27.1)	0.880
Smoking, ever	42 (44)	13 (31)	29 (54)	0.026
Comorbidities	37 (39)	12 (29)	25 (46)	0.077
Hypertension	11 (12)	6 (14)	5 (9)	0.440
Diabetes mellitus	3 (3)	0 (0)	3 (6)	0.120
Chronic lung disease	6 (6)	1 (2)	5 (9)	0.170
T-cell immunity at baseline	73 (76)	33 (79)	40 (74)	0.610
CD4 + reactive	67 (70)	28 (67)	39 (72)	0.560
CD8 + reactive	62 (65)	31 (74)	31 (74)	0.710
Past COVID-19 diagnosis at baseline			–	–
Asymptomatic infection	3 (3)	3 (7)	–	–
Mild disease	27 (28)	27 (64)	–	–
Moderate disease	5 (5)	5 (12)	–	–
Severe disease	7 (7)	7 (17)	–	–
History of positive RT-PCR at baseline	35 (36)	35 (83)	–	–
SARS-CoV-2 IgG positive at baseline	22 (23)	22 (52)	–	–
Time from COVID-19 to first vaccine dose [days]	306 (290–312)	306 (290–312)	–	–
Time from inclusion to vaccination [days]				
First dose	101 (87–114)	102 (87–118)	101 (84–112)	0.910
Second dose	122 (108–135)	123 (108–139)	122 (105–133)	0.930

COVID-19, coronavirus disease 2019; HCWs, healthcare workers; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. All categorical variables are expressed as number (%) and quantitative variables as median (p25-p75) unless specified.

mass index (BMI), presence of comorbidities, smoking, alcohol intake, concomitant medications, time of exposure to COVID-19 patients, exposure to aerosol-generating procedures, COVID-19 symptoms and signs (fever, cough, anosmia, diarrhea, headache, or pneumonia), and disease severity. Mild disease was defined as the presence of symptoms attributable to COVID-19 in the absence of shortness of breath, dyspnea on exertion, or abnormal imaging. Moderate disease was defined as evidence of lower respiratory disease during clinical assessment or imaging, with oxygen saturation $\geq$ 94% on room air. Severe disease was considered in case of respiratory rate > 30 breaths per min, oxygen saturation of < 94% on room air, a ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air [PaO$_2$/FiO$_2$] $\leq$ 300, or lung infiltrates > 50% [10]. Additionally, the results of all SARS-CoV-2 RT-PCR and serologic tests performed before inclusion and during follow-up were collected. SARS-CoV-2 infection was defined as a positive RT-PCR test on nasopharyngeal swab, or/ and seroconversion. Incident SARS-CoV-2 infections were self-reported prospectively.

During January-February 2021, 102 participants were vaccinated with two doses of BNT162b2 mRNA COVID-19 vaccine given 21 days apart whether or not had been previously infected. All participants received emails to initiate web-based health surveys after each dose of the BNT162b2 vaccine. A reminder was sent to HCWs that had not answered the survey after 8 weeks of the last dose. Participants were asked about the type and time of onset of reactions elicited by each vaccine dose. Additionally, the survey allowed participants to enter free-text information about their postvaccination experience.

Vaccine-induced reactions were classified as local (pain, swelling, erythema at injection site) and systemic (fatigue, malaise, headache, insomnia, fever or chills, muscle or joint pain, enlargement of lymph nodes, nausea, or rash). For local reactions, the intensity was self-referred as mild (1–3), moderate (4–6), or severe (7–10) [11]. The use of analgesics, anti-inflammatory drugs, or medical attention was described.

HCWs with incident SARS-CoV-2 infection between blood collection and second vaccine dose were excluded to avoid misinter-

pretation of vaccine-induced reactions. We divided HCWs into two groups according to their history of SARS-CoV-2 infection at baseline. Secondarily, we compared individuals by the presence of pre-existing cellular immunity, as follows: (A) HCWs with past SARS-CoV-2 infection and pre-existing cellular immunity; (B) HCWs with past SARS-CoV-2 infection without pre-existing cellular immunity; (C) HCWs without past SARS-CoV-2 infection (negative RT-PCR and repeated IgG/A/M serologies) with pre-existing cellular immunity (infection-naïve cross-reactive group), and (D) HCWs without past SARS-CoV-2 infection (infection-naïve) nor pre-existing cellular immunity.

The study was approved by our ethics committee (EC162/20) and registered at the clinical trials repository (clinicaltrials.gov, NCT04402827). Written informed consent was obtained from all participants.

2.1. Laboratory procedures

The presence of cellular immune response was assessed at inclusion. SARS-CoV-2-specific CD4 + and CD8 + T-cells were measured using in vitro stimulation with SARS-CoV-2 peptide pools of viral proteins encompassing the spike, membrane, and nucleocapsid, followed by quantitation of CD4 + and CD8 + T-cell specific interferon (IFN)-γ in live-cell flow cytometry, using peripheral blood mononuclear cells (PBMCs) samples from all participants.

In detail, ethylenediaminetetraacetic acid (EDTA)-blood samples were collected from all individuals. After centrifugation at 200g for 10 min, plasma fraction was collected and again centrifuged at 1200g for 15 min, aliquoted, and stored at −80 °C. The cellular fraction was diluted with phosphate-buffered saline (PBS) and subjected to Ficoll density gradient centrifugation at 500g for 20 min. PBMCs were washed and frozen in fetal bovine serum (FBS) with 8% dimethyl sulfoxide (DMSO, Sigma, USA) in liquid nitrogen.

PBMCs were thawed and plated in 96-well flat-bottom plates at 10^6 cells/well in RPMI-1640 culture medium (Gibco, USA) supplemented with 10% human serum (AB serum, Sigma), 100 IU of penicillin/streptomycin/mL (Gibco, USA), 2 mM L-glutamine, and after
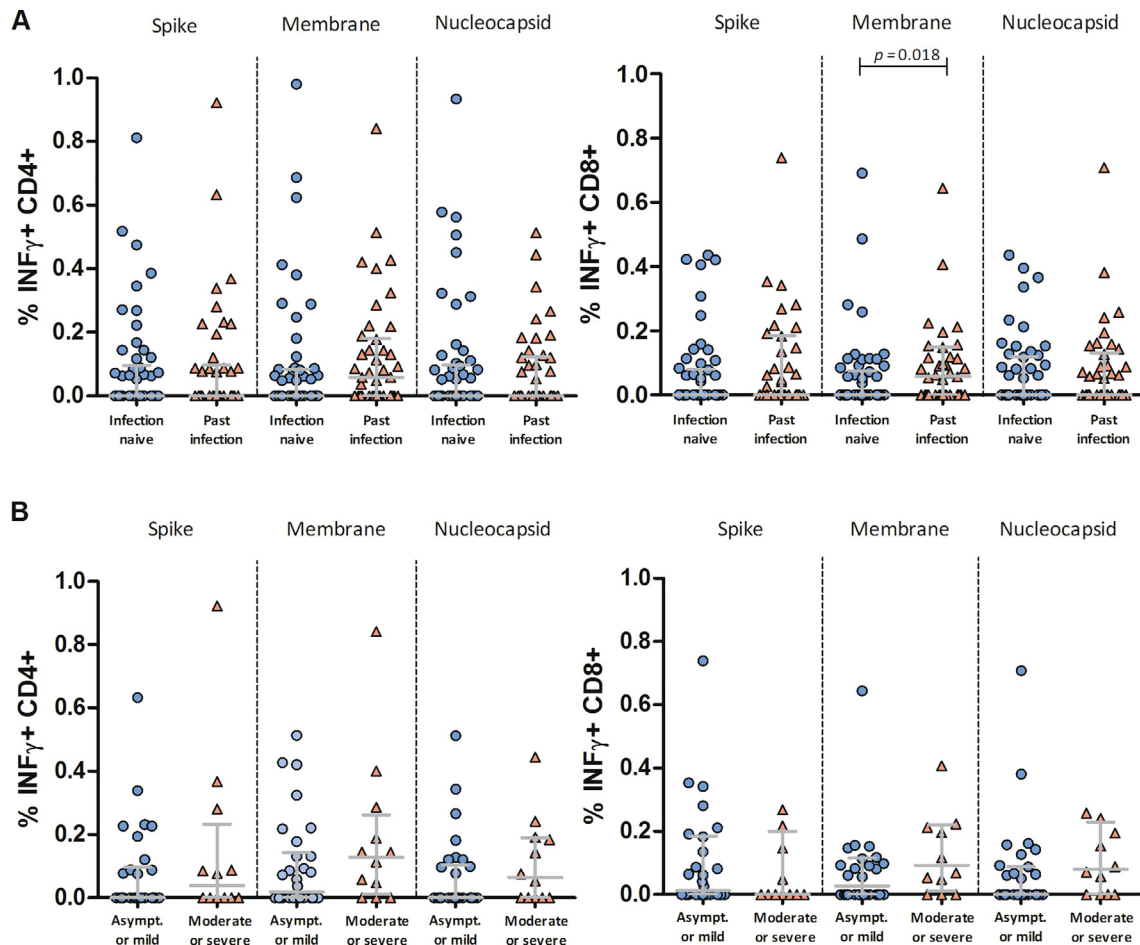
Fig. 1. Quantitative analysis of SARS-CoV-2-specific T-cell immunity in healthcare workers before vaccination according to past infection. Percentage of interferon gamma-producing (INFγ +) CD8 + and CD4 + T-cells induced by peptides spanning the immunogenic domains of the SARS-CoV-2 spike, membrane, and nucleocapsid proteins in peripheral blood mononuclear cells of healthcare workers before vaccination. Data are stratified by history of SARS-CoV-2 infection among all participants (A), and by disease severity among participants with past infection (B). Asympt. = asymptomatic SARS-CoV-2 infection. The horizontal lines represent medians with interquartile ranges. Comparisons between groups were performed using the Mann-Whitney *U* test.

24 h cells were stimulated in five different conditions in the presence of 1 μg/ml purified anti-CD28 antibody (Miltenyi, Germany). Three wells were stimulated with each of the SARS-CoV-2 peptide pools S, M, and N at a concentration of 1 μg/ml. Each peptide pool was composed of 15-mers sequences with 11 amino acids overlap, covering the immunodominant sequence domains of the surface glycoprotein spike, the complete sequence of the membrane glycoprotein, and the complete nucleocapsid phosphoprotein of SARS-CoV-2 (PepTivator SARS-CoV-2 Prot S, M, and N, Miltenyi-Biotec, Cologne, Germany). In addition, one well was stimulated with culture medium alone as a negative control (unstimulated), and another well was stimulated adding 1.5 mg staphylococcal enterotoxin B (SEB, Sigma, Germany) as the positive control. An unresponsive sample to SEB would be excluded from the analysis. Stimulated PBMCs were incubated for two hours before adding brefeldin A (Rapid Cytokine Inspector CD4/CD8 T-cell kit, Miltenyi, Germany) into the medium to stop cytokine release and kept in culture for other 14 h. After stimulation, staining of the cells was carried out with the following fluorochrome-conjugated antibodies using Rapid Cytokine Inspector CD4/CD8 T-cell kit (Miltenyi, Germany): CD3-VioBlue, CD4-APC, CD8-FITC, CD14-PerCP, CD20-PerCP, IFN-γ-PE, and FcR blocking reagent. To exclude dead cells, viability 405/520 fixable dye staining (Milteny, Germany) was added for the last 10 min of incubation. Fixation and permeabilization were performed according to the manufactureŕs protocol.

Samples were measured and analyzed by flow cytometry on a MACSQuant Analyzer 10 using MACSQuantify software. At least 105 cells were analyzed and gated with the following strategy: single (FSC-A/FSC-H dot plot) and live cells were first selected. Cell debris, monocytes, and B cells were excluded from the analysis with CD14- and CD20-PerCP antibodies. Then, lymphocytes were selected with an FSC-A/SSC-A dot plot, and CD3 + T-cells were gated. IFN-γ expression was finally analyzed separately for CD4 + and CD8 + T-cells and it was considered significantly reactive if the proportion of positive cells in stimulated wells was at least 2-fold higher in comparison with the negative control wells (unstimulated). Individuals with pre-existing cellular immunity were defined as those with significant T-cell reactivity to proteins S, M, and/or N.

2.2. Statistical analysis

Characteristics of HCWs were presented globally, by past SARS-CoV-2 infection and by pre-existing cellular immunity to SARS-CoV-2. Continuous variables were expressed as the median, 25th, and 75th percentiles or mean and ranges, as specified. Categorical variables were displayed as frequencies and percentages. Comparisons between groups were performed using two-tailed statistical tests, χ2 or Fisher's exact tests for categorical variables where appropriate, and Mann-Whitney *U* test for continuous variables.
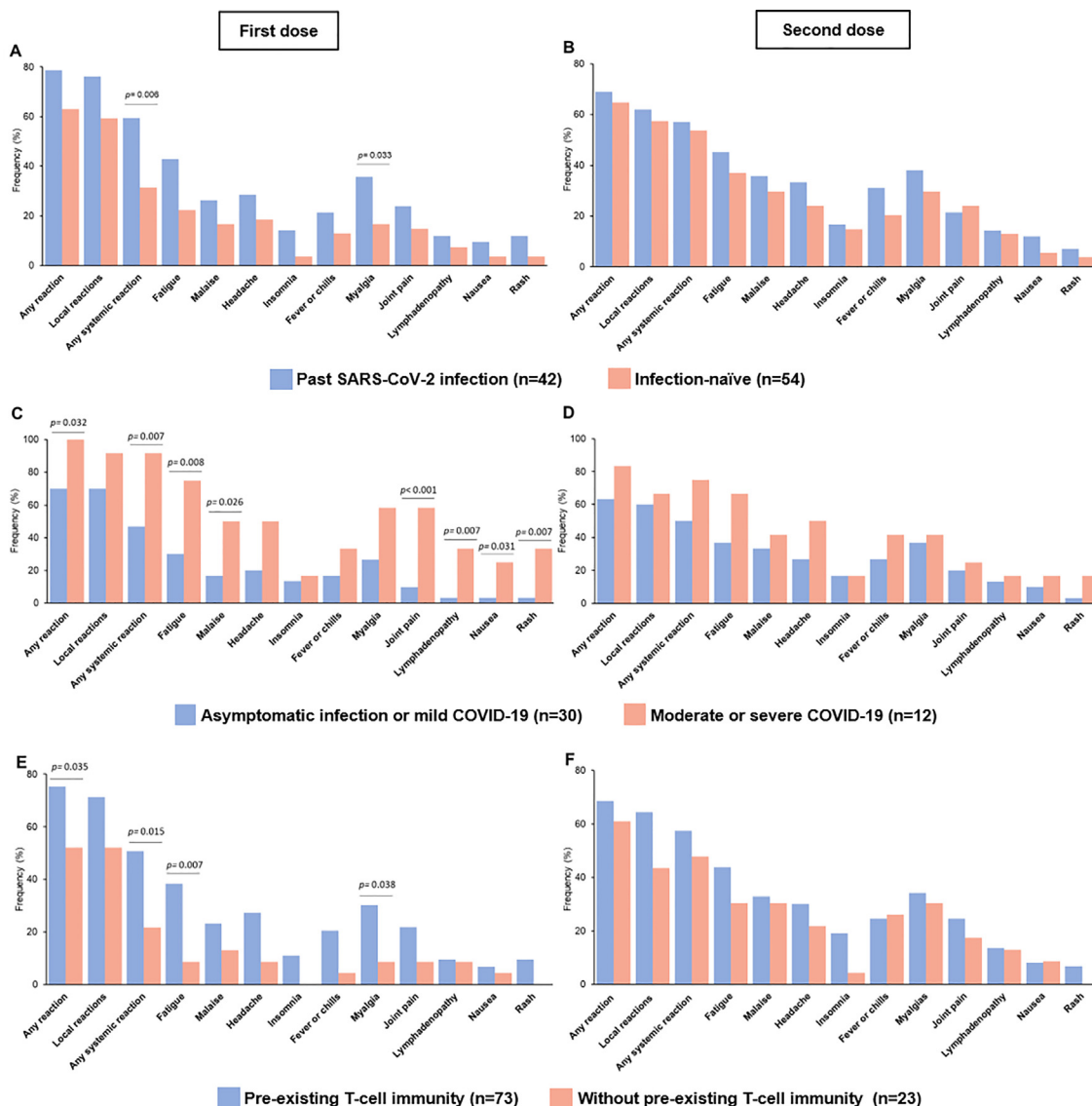
Fig. 2. **Reactogenicity of BNT162b2 mRNA COVID-19 vaccine among healthcare workers.** Comparison of vaccine-induced local and systemic reactions after the first dose (A, C, and E) and second dose (B, D, and F) of BNT162b2 mRNA vaccine. Data are presented as percentages and stratified by history of SARS-CoV-2 infection (A and B), COVID-19 severity (C and D), and pre-existing cellular immunity (E and F). Comparisons between groups were performed using the Mann-Whitney *U* test.

Relative risks (RR) with 95% confidence intervals (95 %CI) of presenting systemic reactions according to subgroups of participants were calculated. Statistical significance was defined as two-sided P-values < 0.05. Statistical analyses were performed by Stata 16.0 software (StataCorp, College Station, TX, USA).

3. Results

A total of 96 HCWs completed the survey and were included in this analysis. The mean age was 44 years (range 26–65) and 66% were females. At baseline, 54 (56%) participants were infection-naïve and 42 (44%) had past SARS-CoV-2 infection, of whom 3 (7%), 27 (64%), 5 (12%), and 7 (17%) had asymptomatic infection, mild, moderate, and severe COVID-19, respectively (Table 1). Using *in vitro* stimulation of PBMCs with SARS-CoV-2 spike, nucleocapsid, and membrane peptide pools, we observed that 73 (76%) participants had pre-existing T-cell immunity to any SARS-CoV-2 peptides, of which 33 had been previously infected and 40 were considered to have cross-reactive responses. Interestingly, the percentage of spike, membrane, and nucleocapsid-specific INFγ + CD4 + and INFγ + CD8 + T-cells was not significantly different

between participants with cross-reactivity and those with past infection, except for membrane-specific INFγ + CD8 + T-cells, which were higher in HCWs with past infection (Fig. 1A). Similarly, HCWs with a history of asymptomatic infection or mild COVID-19 and those with moderate or severe COVID-19 had comparable percentages of virus-specific INFγ + CD4 + and INFγ + CD8 + T-cells (Fig. 1B).

Globally, 73 (76%) HCWs presented any reaction after vaccination (first dose: 70%, second dose: 67%). Most participants reported local reactions (first dose: 67%, second dose: 59%) or systemic reactions (first dose: 44%, second dose: 55%). The most frequently reported symptoms were injection site reactions, fatigue, and myalgias after both doses. No event resulted in hospitalization or death. The rate of local and systemic symptoms after any vaccine dose was similar for participants with past SARS-CoV-2 infection compared with infection-naïve participants (79% versus 74%, *p* = 0.61). However, HCWs with past SARS-CoV-2 infection had a significantly higher frequency of systemic reactions after the first vaccine dose compared with infection-naïve participants (60% versus 31%, *p* = 0.006, Fig. 2A). Indeed, among HCWs with past SARS-CoV-2 infection, reactogenicity after the first dose was significantly

Table 2
Reactogenicity of BNT162b2 mRNA COVID-19 vaccine according to past SARS-CoV-2 infection and pre-existing cellular immunity.

	All groups (n = 96)	Past SARS-CoV-2 infection			Infection-naïve		
		Pre-existing cellular immunity (n = 33)	Without pre-existing cellular immunity (n = 9)	*p*-value	Pre-existing cellular immunity (n = 40)	Without pre-existing cellular immunity (n = 14)	*p*-value
Reactions after any dose							
Any reaction	73 (76)	27 (82)	6 (67)	0.326	30 (75)	10 (71)	0.793
Local reactions (pain, swelling or erythema)	70 (73)	27 (82)	6 (67)	0.326	29 (73)	8 (57)	0.287
Systemic reactions	62 (65)	24 (73)	5 (56)	0.323	26 (65)	7 (50)	0.322
Reactions after the first dose							
Any reaction	67 (70)	27 (82)	6 (67)	0.326	28 (70)	6 (43)	0.070
Local reactions (pain, swelling or erythema)	64 (67)	26 (81)	6 (67)	0.449	26 (65)	6 (43)	0.147
Systemic reactions	42 (44)	21 (64)	4 (44)	0.298	16 (40)	1 (7)	0.023
Use of analgesic or anti-inflammatory drugs	33 (34)	16 (49)	4 (44)	0.737	12 (30)	1 (7)	0.231
Reactions after the second dose							
Any reaction	64 (67)	25 (76)	4 (44)	0.072	25 (63)	10 (71)	0.547
Local reactions (pain, swelling or erythema)	57 (59)	23 (70)	3 (33)	0.046	24 (60)	7 (50)	0.515
Systemic reactions	53 (55)	20 (61)	4 (44)	0.385	22 (55)	7 (50)	0.747
Use of analgesic or anti-inflammatory drugs	48 (50)	21 (64)	3 (33)	0.658	18 (45)	6 (43)	0.490

COVID-19, coronavirus disease 2019; HCWs, healthcare workers. All categorical variables are expressed as numbers (%). Comparisons between groups were performed using two-tailed statistical tests, $\chi2$ or Fisher's exact tests for categorical variables where appropriate.

higher for participants with previous moderate or severe COVID-19 compared with those with asymptomatic or mild infection (any reaction: 100% versus 70%, *p* = 0.032; systemic reactions: 92% versus 47%, *p* = 0.007, respectively; Fig. 2**C**).

Likewise, HCWs with pre-existing cellular immunity to SARS-CoV-2 peptides had significantly greater reactogenicity after the first dose compared with participants without pre-existing cellular immunity (75% versus 52%, *p* = 0.035; Fig. 2**E**). Particularly, systemic reactions such as fatigue, myalgias, and headache were more often observed among HCWs with pre-existing cellular immunity. Fever, rash, and lymphadenopathy were also more commonly reported after the first dose by participants with pre-existing cellular immunity, although it was not statistically significant given the small sample size (Fig. 2**E**). Furthermore, in a subgroup analysis among infection-naïve HCWs, participants with cross-reactivity had a higher risk of systemic reactions after the first dose compared with those without cellular immunity (RR 5.6, 95 %CI 0.82–38.44, Fig. 4 and Table 2).

The percentage of systemic reactions after the second dose was numerically greater than after the first dose (Table 2). Specifically, infection-naïve HCWs and those without pre-existing cellular immunity had a 1.7 and 2.0-times higher rate of systemic reactions after the second dose, respectively (Fig. 2**B** and **F**). Moreover, infection-naïve participants had a higher risk of systemic reactions exclusively after the second dose compared to those with past infection (RR 3.11, 95 %CI 1.12–8.62, Fig. 4). Other comparisons between subgroups of HCWs yielded similar rates of systemic reactogenicity after the second vaccine dose (Fig. 4 and Table 2).

In the quantitative analysis of pre-existing T-cell immunity, percentages of virus-specific INFγ + CD4 + and INFγ + CD8 + T-cells were higher among participants who developed systemic reactions after the first dose (Fig. 3**B**), while they were comparable among HCWs with and without systemic symptoms after the second dose (Fig. 3**D**). Percentages of virus-specific T-cells among participants with and without local reactions after each vaccine dose were similar (Fig. 3**A and C**).

4. Discussion

This study performed in a real-life setting indicates for the first time to our knowledge a close association between pre-existing cellular immunity to SARS-CoV-2 and BNT162B2 mRNA COVID-

19 vaccine reactogenicity. Indeed, 78% of all reactogenicity was attributable to detectable T-cell responses before vaccination. This observation was illustrated by the predominance of systemic reactions after the first dose in HCWs with pre-existing cellular immunity secondary to past infection or cross-reactivity. Moreover, infection-naïve participants were more likely to have systemic reactions only following the second dose, when the adaptive immune response has already been primed.

We found an overall frequency of self-reported reactions to the BNT162b2 mRNA COVID-19 vaccine of 76%, mainly local reactions, fatigue, and myalgia. These observations are consistent with the results of phase 3 clinical trials and nationwide surveillance reports [1,4]. Recently, a large-scale study in the UK reported that females, people aged 55 years or younger, and individuals with prior COVID-19 were more likely to have systemic reactions than males, people older than 55 years, or SARS-CoV-2 naïve individuals, respectively [5]. Although the sample size precluded us to perform age-stratified analysis, our data confirm that individuals with past infection are expected to have reactogenicity. This is in line with previous observations of greater antibody titers and stronger T-cell responses after a single BNT162b2 vaccine dose in individuals with past COVID-19 compared with infection-naïve individuals, indicating secondary memory responses to SARS-CoV-2 antigens [12,13]. Since only six individuals of our cohort had SARS-CoV-2 infection within the six months before vaccination, we were unable to assess the influence of time since COVID-19 infection on reactogenicity.

Notably, reactogenicity after the first vaccine dose was particularly higher among individuals who had presented a moderate or severe disease. Broader and more durable T-cell responses have been described in individuals with a severe disease which may be the result of higher viral loads or dysfunctional T-cell responses and may contribute to disease severity [14,15]. Though, the percentage of SARS-CoV-2 specific T-cells before vaccination was not different based on COVID-19 severity in our small cohort.

Furthermore, we observed that systemic reactions after the first dose were more frequent among individuals with pre-existing cellular immunity to SARS-CoV-2, even among infection-naïve participants. Indeed, individuals with systemic reactions after the first dose had stronger virus-specific CD4 + and CD8 + T-cell responses before vaccination than those without systemic symptoms. Kramer *et al.* described that seropositive vaccine recipients had a higher
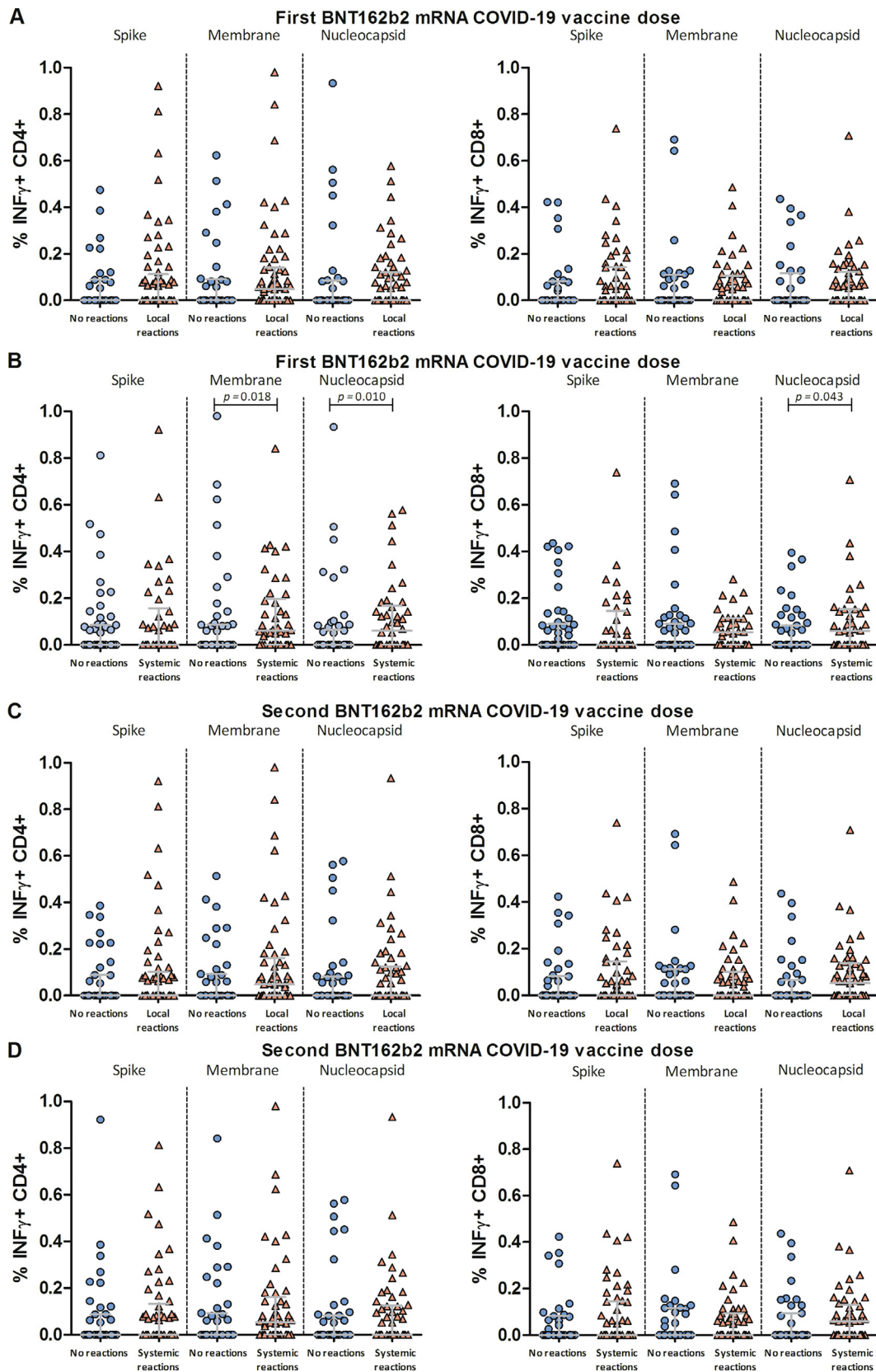
Fig. 3. Quantitative analysis of SARS-CoV-2-specific pre-existing T-cell immunity in healthcare workers with and without BNT162b2 mRNA COVID-19 vaccine reactogenicity. Percentage of interferon gamma-producing (INFγ +) CD8 + and CD4 + T-cells induced by peptides spanning the immunogenic domains of the SARS-CoV-2 spike, membrane, and nucleocapsid proteins in peripheral blood mononuclear cells of healthcare workers before vaccination. Data are presented as self-reported local (A and C) and systemic reactions (B and D) after the first (A and B) and second (C and D) vaccine doses. Comparisons between groups were performed using the Mann-Whitney *U* test.

A   **Systemic reactions after first BNT162b2 mRNA COVID-19 vaccine dose**

B   **Systemic reactions after second BNT162b2 mRNA COVID-19 vaccine dose**
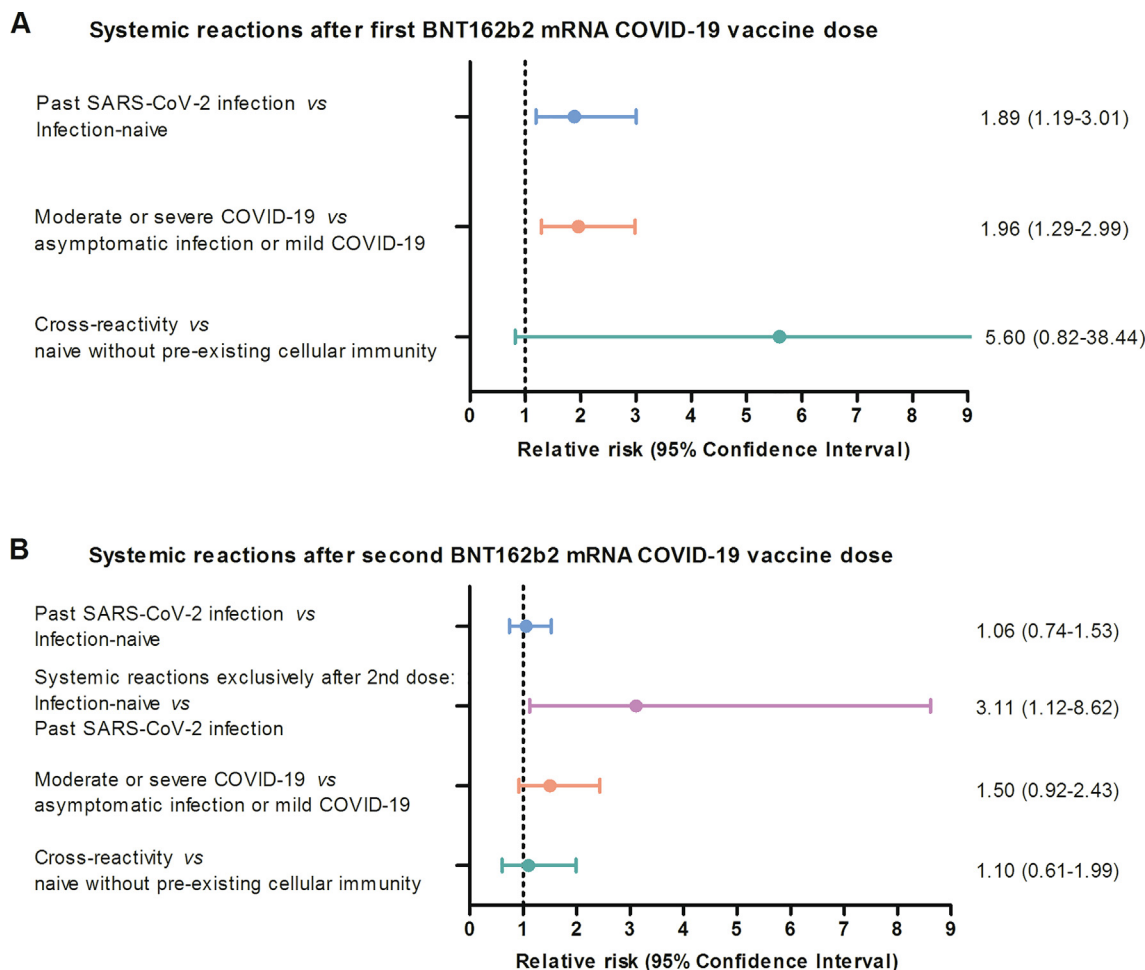
Fig. 4. Risk of presenting systemic reactions after the BNT162b2 mRNA COVID-19 vaccine among healthcare workers by subgroups. Relative risk and 95% Confidence Interval for comparisons based on history of SARS-CoV-2 infection, COVID-19 severity, and pre-existing cellular immunity for the first (A) and second (B) vaccine dose.

rate of systemic events than seronegative individuals suggesting a correlation between humoral immunity and reactogenicity [16]. However, reports of cellular correlates of reactogenicity for SARS-CoV-2 vaccines as well as other vaccines are scarce [17]. Burny *et al.* observed associations between the CD4 + T-cell responses elicited by hepatitis B virus surface antigen combined with different adjuvants and systemic reactions [17]. Globally, our data demonstrate that BNT162b2 mRNA vaccine-induced systemic reactogenicity is explained by the presence of cellular immunity before vaccination either in individuals with past SARS-CoV-2 infection and in those with cross-reactive T-cell responses. In these individuals, the first vaccine dose acts as a booster dose that enhances immunity and therefore leads to reactogenicity [12].

Consistent with previous results, systemic reactions were more frequent after the second dose of the BNT162b2 mRNA vaccine [1,4]. Our findings further indicate that the increment in systemic reactogenicity after the second dose occurs mainly among infection-naïve individuals and those without pre-existing cellular immunity. This is supported by the notion that the second vaccine dose predominantly boosts the adaptative immunity among infection-naïve individuals [18,19]. Alternatively, it may reflect a contraction of cellular immunity after the second dose in previously infected individuals due to activation-induced cell death or functional exhaustion, as hypothesized by Camara *et al* [19]. Although the amount of virus-specific T-cells before vaccination was similar in individuals with and without reactogenicity after

the second dose, we did not analyze T-cell responses in the period between the first and second doses which might have detected differences between subgroups.

Our study has several limitations, including the small sample size and the relatively young mean age of our population, precluding the generalization of results to older populations. Second, HCWs with past infection might have been misclassified as being infection-naive considering that some individuals do not build humoral or cellular responses after SARS-CoV-2 infection. However, this issue was minimized by repeating highly sensitive serological tests.

In conclusion, most of BNT162b2 mRNA COVID-19 vaccine reactogenicity is attributable to pre-existing cellular immunity to SARS-CoV-2 either elicited by prior COVID-19 or cross-reactivity. Further studies should demonstrate whether reactogenicity is also related to vaccine immunogenicity. Anyway, our findings provide insights into the mechanisms underlying vaccine-induced reactions and may reduce negative attitudes towards vaccines that challenge their impact on public health.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contribution

Pilar Vizcarra: Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Johannes Haemmerle:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Hector Velasco:** Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Tamara Velasco:** Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Marina Fernández-Escribano:** Conceptualization, Investigation, Validation, Visualization, Writing – review & editing. **Alejandro Vallejo:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. **José L. Casado:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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