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Short communication

Safety of Pfizer-BioNTech vaccine in a cohort of healthcare providers: Differences between naïve and previously infected by SARS-CoV-2

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Abstract

Introduction: The Spanish Society of Immunology recently warned that a history of past COVID-19 could result in a higher incidence of adverse events (AEs) related to vaccination. We set out to analyze whether there were any differences in AEs between healthcare workers vaccinated for COVID-19 (either after the first or second dose) who had had a prior diagnosis SARS-CoV-2 infection at any time compared to those who had not had COVID-19 before vaccination.

Methods: This was a retrospective cohort study in a population of healthcare workers. AEs related to the first and second doses of the Pfizer vaccine were recorded. We compared the incidence of AEs and compared individuals with 0–3 different AEs to those with 4 or more AEs. The relative risks (RR) and their 95% confidence intervals were calculated.

Results: Past infection was associated with having more AEs after the first dose \((p < 0.001)\), but not the second one \((p = 0.476)\), as well as a higher incidence of AEs \((p < 0.001)\). Common AEs that were statistically associated with past COVID infection included arthralgia, asthenia, fever, chills, headache, and myalgia \((p < 0.001)\). The RR for having an increased absolute number of different AEs was 1.18 \((95\% CI [1.05, 1.33])\) after the first dose and 1.05 \((95\% CI [0.96, 1.14])\) after the second dose. The maximum number of days between past infection and vaccination was 306.

Conclusions: Our results showed that the incidence of AEs was higher in individuals with a history of prior COVID-19 infection.

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1. Background

The COVID-19 pandemic, which originated in Wuhan in December 2019, is causing enormous human and economic costs. By the end of April 2020, more than 3 million cases had been confirmed in Spain, with more than 75,000 COVID-19-related deaths [1]. Spain’s Covid-19 vaccination campaign [2], which started on December 27, 2020, prioritizes population groups according to their vulnerability and risk of exposure. The vaccinations started with elderly people in nursing homes, followed by healthcare workers, people with disabilities who required intensive support, and then the rest of the population according to their age and comorbidities.

The Consorcio Hospital General Universitario de Valencia (CHGUV) is a level-three hospital which attends to more than 19,000 patients per year. The CHGUV has 3,648 healthcare workers, of which 468 had been diagnosed with COVID-19 as of January 26, 2021. The vaccination campaign for frontline workers at the CHGUV with the Pfizer-Biotech vaccine started on January 9, 2021 and did not differentiate between patients with a previous history of COVID-19 or not.

According to the vaccine fact sheet [3], the most common adverse events (AEs) related to this vaccine are injection site pain, fatigue, headache, myalgia, arthralgia, and fever. These AEs are generally mild or moderate and resolve a few days after the vaccine administration. At the end of January 2021, the Spanish Society of Immunology [SEI] [4] warned that the immune reaction to the vaccine among people who had had COVID-19 seemed to be more vigorous and could result in an increased incidence of AEs.

Thus, in this work we analyzed whether there were any differences in the incidence of AEs in healthcare workers vaccinated for COVID-19 (either after the first or second dose) who had had a prior diagnosis SARS-CoV-2 infection compared to those who had not had COVID-19 before vaccination.
A retrospective cohort study was designed by the epidemiology department at the CHGUV. All the healthcare workers who had previously been diagnosed with COVID-19 (n = 107) were selected for the sample along with 3 times as many age and sex-matched workers without a prior history of COVID-19 (n = 321). The injectable COVID-19 mRNA vaccine Comirnaty® concentrate was correctly diluted and the recommended interval of up to 21 days between the first and second dose was respected in every case.

Data about AEs after the first dose of the vaccine were collected via a survey completed by healthcare staff immediately after the administration of their second dose. Moreover, according to clinical practice procedures, 5 days after the second dose, we also contacted every hospital worker who had been vaccinated (by telephone) to specifically ask about joint pain, asthenia, fever, chills, headache, muscle pain, nausea, injection site pain, erythema, and other possible side effects of the second dose.

We performed a descriptive analysis of the sample and the variables of age, sex, COVID-19 diagnosis, and number of days elapsed between the diagnosis and the vaccination. Chi-squared tests were used to evaluate the incidence of any AEs and to assess the differences between groups with 0–3 symptoms (absolute number of different AEs) and those with 4 or more symptoms. Finally, we used Student t-tests to check for any differences in the number of days since the diagnosis and the vaccination. The relative risks (RR) for having a higher absolute number of different AEs and their 95% confidence intervals were calculated. All the analyses were performed using Stata software (StataCorp. 2019, Stata Statistical Software: Release 16. College Station, TX, StataCorp LLC.).

2. Methods

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3. Results

We included 101 healthcare workers who had had a COVID-19 diagnosis and 305 others without a prior diagnosis of COVID-19; 22 healthcare workers were excluded because they did not complete the follow-up. The distribution by sex was 279 (68.6%) women and 127 (31.4%) men, and the average age of the whole sample was 43.1 years. Moreover, it was only possible to use the data from the first dose for 36 of the healthcare workers because they had subsequently been diagnosed with COVID-19 before the second dose. The individuals with a prior diagnosis of COVID-19 had been infected a mean of 128.95 days (±306 to 13) before the first vaccine dose was administered. An average of 6.7 days had elapsed since the vaccination in the individuals diagnosed with COVID-19 after the first vaccine dose.

All the AEs observed were divided into local or systemic effects categories. The minimum number of AEs was 0 and the maximum was 7. The mean of local AEs was 0.7 for the first dose and 0.7 for the second dose; the mean of systemic AEs was 0.5 for the first dose and 1.7 for the second dose. Both for the first and second dose, the most frequent systemic effects were headache (16.5% and 32.4%, respectively) and asthenia (8.4% and 37.6%, respectively). Other symptoms reported were axillary adenopathy, diarrhea, sore throat, dizziness, eye pain, and drowsiness; all of them with an incidence lower than 1%.

The individuals who had previously had COVID-19 experienced significantly more AE symptoms after the first dose (p < 0.001) than after the second dose (p = 0.476). The relationship between all AEs and the presence or absence of disease was also statistically significant (p < 0.001). The RR for having a higher absolute number of different AEs were 1.18 (95 %CI [1.05,1.33]) after the first dose and 1.05 (95 %CI [0.96, 1.14]) after the second dose.

Having had a prior diagnosis of COVID-19 was associated with arthralgia (p < 0.001), asthenia (p = 0.001), fever (p < 0.001), chills (p < 0.001), headache (p < 0.001), and muscle pain (p < 0.001) after the first dose (Table 1), but none of the most common AEs were significantly associated with the second dose in these patients. We found no association between the mean number of days from diagnosis to vaccination and the incidence of fewer (−190.91 days) or more AEs (−250.73 days, p = 0.067, 95% CI [−4.23, 123.87]).

4. Discussion

Vaccination is the most effective medical intervention that has ever been introduced, although an effective vaccine usually requires more than one immunization in the form of a booster injection. In our study, the incidence of AEs in healthcare personnel was higher after the second dose than with the first one, which coincides with the safety and efficacy findings for the BNT162b2 mRNA Covid-19 Vaccine [5].

Our study demonstrated that incidence of AEs was higher in individuals with a history of past SARS-COV-2 infection than those with no history of the disease. The onset of symptoms was observed mainly on the first day after vaccination. We found a significant difference in the incidence of AEs after the first vaccine dose in health personnel who had had a SARS-Cov-2 infection, but no differences after the second dose. This effect may be because the first dose acts as if it were a booster injection in patients who had previously had SARS-COV-2.

Because this is a new topic, very few related studies are available in the academic literature. To date, studies on AEs have approached the problem in terms of serological response without...
specifically focusing on AEs. Of the articles related to our topic, Krammer et al. [6] found that 159 of their 231 participants experienced AEs; 66% had no history of COVID-19 infection and 73% had had COVID-19. In contrast, we found an increase in AEs after the first vaccine dose, with 308 of the 406 healthcare workers reporting AEs, 58% of them with a history of COVID-19. The most common AEs in both these studies were arthralgia, asthenia, fever, chills, headache, and muscle pain.

Finally, despite these interesting findings, some limitations to this study must be considered. First, this was a retrospective study and so some memory bias may have occurred, especially considering that 21 days had passed when the data about the first-dose symptoms were collected. Second, some healthcare workers may have suffered an asymptomatic and undiagnosed SARS-COV-2 infection. In this context, updated data from the ENE-COVID study [7] conducted by the Carlos III Institute of Health (Spanish Ministry of Science) and Ministry of Health estimates that the prevalence of IgG antibodies against SARS-CoV-2 in healthcare workers was 11.2%. Nonetheless, our data support the SEI premise that more AEs may present in people who have already had COVID-19, especially after the first vaccine dose.

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.

References

[1] Health Alert and Emergency Co-ordination Centre (CCAES), Ministry of Health, Consumer Affairs and Social Welfare. Actualización n° 321. Enfermedad por el coronavirus (COVID-19). 26.02.2021 Available at: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Actualizacion_321_COVID-19.pdf.
[2] Interterritorial Council of the National Health System. Vaccination strategy against COVID-19 in Spain. COVID-19 Technical Vaccination Working Group, Vaccination Program and Registration Presentation; 2 December 2020. [consulted the 17/1/2021]. Available at www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/docs/Covid-19_EstrategiaVacunacion.pdf.
[3] EMA COVID-19 vaccine safety update 28/01/2021COMIRNATY BioNTech Manufacturing GmbH. Available at https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-comirnaty-january-2021_en.pdf.
[4] Spanish Society of Immunology (SEI). Positioning of the Spanish Society of Immunology (SEI) on vaccination in patients who have already overcome COVID-19. Link to report: https://www.immunologia.org/index.php/covid-19.2021.
[5] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383 (27):2603–15.
[6] Krammer F, Srivastava K. PARIS team, Simon V. Robust spike antibody responses and increased reactogenicity in seropositive individuals after a single dose of SARS-CoV-2 mRNA vaccine. N Engl J Med 2021; 384: 1372-1374 Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2101667
[7] Institute of Health Carlos III, Ministry of Science and Innovation, Ministry of Health, Consumer Affairs and Social Welfare. Estudio ENE-COVID: Cuarta Ronda Estudio Nacional de sero-epidemiología de la Infección por Sars-CoV-2 en España. Available at: https://www.mscbs.gob.es/gabinetePrensa/notaPrensa/pdf/15.12151220163348113.pdf.