

# SARS-CoV-2 breakthrough infection after artificial and hybrid immunization in healthcare workers

DOI: 10.5377/alerta.v5i2.14395

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### Infección por SARS-CoV-2 posterior a la inmunización artificial e híbrida en el personal de salud

#### Suggested citation:

López Contreras JE, Castillo Vélez FE, Murguía Gutiérrez G, Sepúlveda Marrón J, Sánchez Martínez EP, Paredes Casillas P. SARS-CoV-2 breakthrough infection after artificial and hybrid immunization in healthcare workers. *Alerta*. 2022;5(2):118-125. DOI: 10.5377/alerta.v5i2.14395

#### Received:

February 3, 2022.

#### Accepted:

June 22, 2022.

#### Published:

July 20, 2022.

#### Author contribution:

JELC<sup>1</sup>: conception of study, writing, revision and edition. FECV<sup>2</sup>: manuscript design and data analysis. GMG<sup>3</sup>: bibliography search. JSM<sup>4</sup>: data collection. EPSM<sup>5</sup>: data management. PPC<sup>6</sup>: writing, revision and edition.

#### Conflicts of interest:

The authors declare there are no conflicts of interest.

### Abstract

**Introduction.** Current reports suggest that people with a history of SARS-CoV-2 infection and a complete vaccination status have greater protection against the symptomatic presentation of SARS-CoV-2. **Objective.** To compare the risk of becoming ill with COVID-19 between health personnel with a complete SARS-CoV-2 BNT162b2 vaccine status and a history of SARS-CoV-2 infection. **Methodology.** Historical cohort study in 1874 health workers of the New Civil Hospital of Guadalajara immunized with the BNT162b2 vaccine between January and March 2021. After six months of follow-up, the non-exposed group (without a history of infection) was 1397 and the group exposed (with a history of infection) of 477 subjects. **Results.** The incidence of SARS-CoV-2 infection in the cohort was 39 cases, the risk of infection after immunization was 0,021, the lowest risk was identified in the hybrid immunization group (0,015 and 0,243), with a relative risk of 0,43 (95 % CI 0,17 to 1,09). Hybrid immunization contributed to a population-attributable risk reduction of 0,003 (R0 0,024; Rp 0,020). Hospitalization occurred in 7,69 % of confirmed cases with SARS-CoV-2. The risk of hospitalization in hybrid immunization is 0,210 and 0,143 in the artificial immunization group (RR 1,4 95 % CI 0,13-16,11). **Outcome.** Hybrid immunization could contribute to reducing the risk of infection for future variants of SARS-CoV-2 by enhancing the immunity generated by the vaccine against COVID-19.

### Keywords

COVID, vaccines, reinfection.

### Resumen

**Introducción.** Reportes actuales sugieren que el antecedente de infección por SARS-CoV-2 y completar un esquema de vacunación otorga mayor protección contra la presentación sintomática de COVID-19. **Objetivo.** Comparar el riesgo de enfermar de COVID-19 entre el personal de salud con esquema completo de vacuna contra SARS-CoV-2 BNT162b2 y el antecedente de infección por SARS-CoV-2. **Metodología.** Estudio de cohorte histórica en 1874 trabajadores de la salud del Nuevo Hospital Civil de Guadalajara inmunizados con vacuna BNT162b2 entre enero y marzo de 2021. Después de seis meses de seguimiento, el grupo de no expuestos (sin antecedente de infección) fue de 1397 y el grupo expuesto (con antecedente de infección), de 477 sujetos. **Resultados.** La incidencia de infección por SARS-CoV-2 fue de 39 casos. El riesgo de infección en la cohorte posterior a la inmunización fue de 0,021. El grupo de inmunización híbrida presentó un riesgo menor de infección comparado con el grupo de inmunización artificial (0,015 y 0,243). La inmunización híbrida contribuyó a una reducción del riesgo atribuible a la población de 0,003 (R0 0,024; Rp 0,020). La hospitalización se presentó en el 7,69 % de los casos confirmados con SARS-CoV-2. El riesgo de hospitalización en inmunización híbrida es de 0,210 y de 0,143 en el grupo de inmunización artificial (RR 1,46 IC95 % 0,13-16,11). **Conclusión.** La inmunización híbrida podría contribuir a reducir el riesgo de infección por SARS-CoV-2, potenciando la inmunidad generada por la vacuna contra COVID-19.

### Palabras clave

COVID-19, vacunas, reinfección.

## Introduction

At the end of 2019 in Wuhan, China, an outbreak of respiratory infection was reported and a new virus, from the coronavirus type 2, was identified as the cause of severe

acute respiratory syndrome (SARS-CoV-2)<sup>1</sup>. On January 13, 2020, the first case outside of China was identified in Thailand; subsequently, the virus rapidly spread globally and was declared a pandemic by the World Health Organization on March 11, 2020<sup>2</sup>.

In Mexico, the first case of infection with the SARS-CoV-2 virus, which causes the Coronavirus disease 2019 (COVID-19, for its acronym from coronavirus disease) was registered on February 27 2020<sup>3</sup>. In Jalisco, thirteen days later, the first two cases were reported, one of them was a worker at the New Civil Hospital of Guadalajara, with the history of having traveled to an area with active community transmission<sup>3</sup>.

The first COVID-19 vaccine, Pfizer-BioNTech (BNT162b2) was authorized by the United States Food and Drug Administration on December 11, 2020. Similarly, in Mexico, the Federal Committee for Protection against Sanitary Risks authorized the emergency use of this vaccine within the national health policy against SARS-CoV-2. The first phase of vaccination started on December 24, 2020 and the first dose was applied in the health personnel of the New Civil Hospital of Guadalajara on January 13, 2021, extending the coverage until August of the same year<sup>4</sup>.

The effectiveness of the second dose of BNT162b2 against SARS-CoV-2<sup>5</sup> infection has been demonstrated. An overall incidence between 0,001 and 0,011 (per 100 persons at risk for developing the infection) has been described in post-vaccination healthcare personnel<sup>6</sup>. The occurrence of infection in health personnel with complete vaccination schedules, specifically with the biological BNT162b2, reported an incidence of infection of 4,4 per 1000 among women and 5,7 per 1000 among men ( $p=0,57$ ) and has been correlated with low neutralizing antibody titers during the peri-infection period<sup>7</sup>.

Factors such as old age, immunosuppression, comorbidities or variants prevalent in population dynamics increase the risk of infection in six months after immunization<sup>8,9</sup>. As long as the pandemic continues, subsequent cases of infection will be a common scenario in the occupationally exposed population. This study compares the risk of COVID-19 over the first six months in relation to have completed the vaccination schedule and have a history of infection.

## Methodology

A historical cohort of health personnel immunized with the SARS-CoV-2 BNT162b2 vaccine was conducted from January to February 2021 at the New Civil Hospital of Guadalajara Dr. Juan I, Menchaca. The population studied included all health personnel registered in the online vaccination platform to complete the scheme with the

application of the second dose of BNT162b2 during February in 2021. From a universe of 2105 subjects, 1874 were included who completed their 2-dose schedule by March 1, 2021.

The subjects were naturally grouped, considering the group not exposed to personnel without the history of SARS-CoV-2 infection ( $n=1397$ ) and the exposed group composed of individuals with a history of SARS-CoV-2 infection ( $n=477$ )

The history of SARS-CoV-2 infection was determined by the history of COVID-19 confirmed by a molecular or immunoassay test, diagnosed prior to the administration of the second dose and referred to in the vaccination registration form, epidemiology records or electronic file. Nursing and medical positions were classified as medical personnel. This study considered subjects with a complete vaccination schedule and no history of primary SARS-CoV-2 infection up to ten days after the application of the second dose were considered as the artificial immunity group. Subjects with a complete vaccination schedule and a history of primary SARS-CoV-2 infection in the 14 days prior to the application of the second dose were defined as the hybrid immunity group.

## Active surveillance and sources of information

Active surveillance of cases of SARS-CoV-2 infection in health personnel was established. A person of any age who in the last ten days has presented at least one of the following signs and symptoms was used as an operational definition of a suspected case of respiratory infection: cough, dyspnea, fever or headache, accompanied by: arthralgias, rhinorrhea, anosmia, among others, which is established in the manual for epidemiological and laboratory surveillance of the viral respiratory disease in force of the General Directorate of Epidemiology of Mexico<sup>10</sup>. Personnel who had symptoms compatible with viral respiratory infection or with a history of recent exposure to an active case of SARS-CoV-2 by the employee medical service were clinically evaluated. Only those cases confirmed by molecular or antigenic tests with the start of symptoms from March 1 to August 31, 2021 were considered an incident case of SARS-CoV-2 infection.

The information obtained from each evaluation and the results of the diagnostic tests were recorded in the epidemiological study of suspected cases of viral respiratory disease<sup>10</sup>. Cases were traced in the data-

bases of the epidemiological survey and the electronic file. The variables that were considered were the following: age, sex, medical personnel, history of diabetes, heart diseases, lung diseases, asthma, smoking, date of application of first and second doses, dates of application of first and second dose, date of symptoms onset and diagnostic test.

The data were analyzed with the free software version R edition 4.0.5. The “dplyr” library was included for data manipulation, means and proportions were estimated for the sample description. The inferential analysis was performed using the Ep R library for the calculation of the risk and hypothesis test of the qualitative variables, performing Fisher’s exact test for the history of lung disease due to the expected values, and for the rest of the qualitative variables, and chi-square test for the rest of qualitative variables, with determination of confidence intervals to evaluate the relative risk, and point probability estimates for proportions.

In the case of age, the Kolmogorov-Smirnov test was used as a hypothesis test to determine the difference in the distribution of the groups because they did not present a normal distribution. Because the data were collected during the institution’s routine operating procedures of standardized epidemiological surveillance, this analysis of secondary data does not require informed consent and was conducted in a consistent manner with applicable federal law on the protection of personal data.

## Results

As of March 1, 2021, the vaccination coverage with full schedule represented 89%. The mean age of the 1874 health workers included in the study was 40,23 years (SD 10,75), with a minimum age of 19 years

and a maximum age of 69 years, showing a bimodal distribution with a predominance of 29 and 48 years, where 36,98% (693) of the registered personnel were male and 29,08% corresponded to non-medical personnel

74,55% (1397) of the subjects were classified in the artificial immunization group (30,1% were non-medical personnel), while 477 (25,45%) had a history of natural infection with SARS-CoV-2, so they were classified as the hybrid immunization group. A significantly higher proportion for the male gender was presented by the artificial immunization group (38,4% compared to 32,9%,  $p=0,033$ ); similarly, age showed a significant difference between the distribution of both groups (KS test  $p=3 \times 10^{-3}$ ) (Table 1). The evaluation of homogeneity of the artificial immunity groups compared to the hybrid immunity group showed a similar distribution for occupation (69,9%; 74,0%), history of diabetes *mellitus* (6,3%; 5,03%), heart disease (2,36%; 2,1%) or pulmonary (0,04%; 0,84%), asthma (5,73%; 7,97%) or smoking (12,5%; 10,5%), without any significant difference for both groups.

The first case of confirmed SARS-CoV-2 infection occurred 99 days after administration of the second dose of the BNT162b2 vaccine, with an average case presentation time of 158,9 days. In the hybrid immunization group, the mean to present infection was 149,20 days, while in the artificial immunization group the mean was 160,32 days (difference -11,12, 95% CI -50,96 to 28,71), with no significant difference between the two groups (Figure 1).

During follow-up, there was an incidence of 39 cases of SARS-CoV-2 with a risk of infection of 0,021 after immunization, a lower risk was identified for the hybrid immunization group (0,015 compared to

**Table 1.** Evaluation of the homogeneity of the groups

	Híbrido inmunity n=477 (%)	Artificial inmunity n=1397 (%)	p
Age†	38,6 (10,50)	40,78 (10,79)	0,003*
Masculine	157 (32,9)	536 (38,4)	0,033*
Medical personnel‡	353 (74,00)	976 (69,9)	0,086
Diabetes	24 (5,03)	88 (6,30)	0,313
Heart disease	10 (2,10)	33 (2,36)	0,738
Lung disease	4 (0,839)	5 (0,0358)	0,244Ω
Asthma	38 (7,97)	80 (5,73)	0,082
Smoking	50 (10,5)	174 (12,5)	0,251

P value estimated by chi-square test.

† The results are shown as mean and standard deviation, the p statistic was estimated using the Kolmogorov-Smirnov two-tailed test, as it did not present normal distribution. \* Value with statistically significant difference. ‡ Medical and nursing posts were considered medical personnel. Ω Using Fisher’s-exact test

0,243), with a relative risk of 0,43 (95 % CI 0,17-1,09). Hybrid immunization contributed to a population-attributable risk reduction of 0,003 (R0 0,024 compared to Rp 0,020). 7,69 % of confirmed cases with SARS-CoV2 received hospital care. The risk of hospitalization for the hybrid immunization group was 0,210 and 0,143 for the artificial immunization group (RR 1,46 95 % CI 0,13-16,11), with no significant difference in the risk of confirmation by SARS-CoV-2 infection or in the evolution of the disease requiring hospitalization. Deaths were not occurred during the follow-up of the cohort.

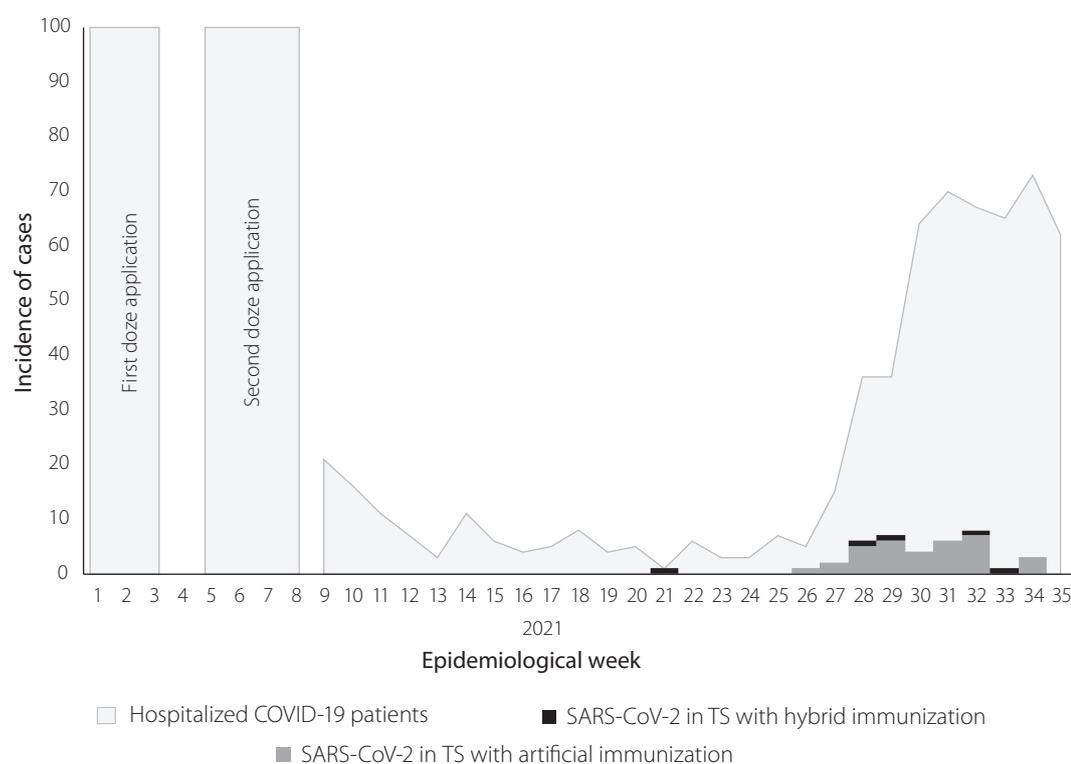
## Discussion

This study reviewed the information recorded in the electronic medical record, the epidemiological background questionnaire and the contact tracing that was installed during the follow-up of health personnel during the six months following the administration of the second dose of the BNT162b2 vaccine in response to an infection prevention and control protocol.

The analysis of the data found a lower proportion of confirmed COVID-19 cases in the hybrid immunization group with a risk reduction of more than 50 %. In the non-medical staff group, the attributable risk in the population and the impact on case reduction was high. Considering this population with a

lower risk of exposure and a prevalence of a history of lower infection than estimated in the group of medical personnel, the impact would be related to the lower occupational exposure<sup>11</sup>. Besides, the implementation of strategies by health personnel with respect to other effective interventions to reduce the risk of infection, such as adherence to personal protection measures, correct use of a mask, social distancing and isolation of sick personnel, would also explain this difference compared to non-medical personnel<sup>12,13</sup>. Therefore, variable compliance with protective measures in the hospital environment and higher immunization coverage among health personnel would explain the lower incidence of SARS-CoV-2 when general population is compared<sup>14</sup>.

The average time of infection in health personnel with a complete vaccination schedule in both groups was similar and there were no cases in vaccinated personnel in both groups during the first three months of follow-up. It is possible that the decrease in cases could be attributable to immunization, as observed by Chodick *et al.*, where one dose of the vaccine was associated with a nearly reduction of 50 % in the risk of SARS-CoV-2 infections in the 25 days following application<sup>15</sup> and even as part of the additional protection against reinfection from one dose in people with a history of COVID-19 subsequent to the vaccine<sup>16</sup>.



**Figure 1.** Incidence of patients treated with COVID-19 and SARS-CoV-2 infection in immunized personnel

Estimating the response to vaccination and protection over time is complex because of its multicausal nature. The protection generated by natural immunity may differ from the immunity generated by the vaccine due to several factors, such as the apparent increase in the immune response due to antigenic exposure with additional boosters in the population with a history of primary infection and a probable protection against variants of concern of SARS-CoV-2<sup>17</sup> due to the induction of higher levels of IgG antibodies and neutralizing antibodies<sup>18</sup>. These neutralizing antibody titers are not available in the Latin American hospital setting/context. Although the use of anti-S IgG titers could be considered as a more accessible method to assess long-term protection, this insufficient immunogenicity of the vaccine may not really be correlated at the time of diagnosis and the development of symptoms with low levels of these neutralizing antibodies and their measurement and therefore not be a good indicator of the progression of the disease or its ability to spread<sup>19</sup>. In this sense, the interaction of multiple epitopes after natural SARS-CoV-2 infection and the particular interaction of vaccines in a single epitope is recognized, with the result of permanent immune protection, due to the diversity of these interactions of long-lived memory T cell populations in hybrid immunity<sup>20</sup>.

The results reinforce the possible increase in protection in health personnel with a history of SARS-CoV-2 infection, probably due to a greater immune response to vaccination, but it is necessary to evaluate the true impact on the general population<sup>21,22</sup>. Also, the results are consistent with what was published by Hall *et al.*, where greater short-term protection against SARS-CoV-2 infection in health workers was associated with a complete BNT162B2 scheme at the follow-up at six months and protection preserved up to one year after vaccination, in the group with a history of primary infection<sup>23</sup>. In this case, hybrid immunization contributed to a reduction in risk attributable to the population of 0,003 (R0 0,024; Rp 0,020), this in relation to a memory protection mediated by the immune system and T cells, although at the time the study was carried out the omicron variant was not in circulation<sup>16</sup>.

A significant difference was found in the sex of the cases related to the evaluation of the groups. Similar findings are commented by other publications and suggest differences in innate and adaptive immune responses, where there is a difference in susceptibility to infections, variations in behavior patterns,

perception and response to pathogens or vaccines, in the frequency and severity of adverse events, but without differences in efficacy or immunogenicity<sup>24</sup>. This difference could be considered due to a greater representation of the female sex in health personnel and their distribution within the health population, which establishes an unequal representation within the study to properly assess these relevant differences between women and men<sup>25</sup>.

During cohort follow-up in the first six months' post-vaccination, deaths were not reported and both groups had very low risks of hospitalization. The BNT162b2 vaccine is an anti-COVID-19 mRNA vaccine. Vaccination with biological anti-COVID-19 mRNA has been shown to decrease the probability of hospitalization, complications or death and are consistent with reducing the risk of infection compared to the absence of vaccination<sup>26</sup>.

Previous studies have documented successful rates for the prevention of symptomatic SARS-CoV-2 infection and protection against general hospitalization with complete vaccination schedules with the BNT162b2 mRNA vaccine with a 90% effectiveness during the protection period in previously healthy individuals<sup>5,27</sup>. The prevention of COVID-19 mortality in health personnel is associated with evidence-based interventions, such as ensuring vaccination coverage, infection monitoring and control programs, procuring hospital capacity and hospitalizations, and specific protection strategies in vulnerable personnel due to age or comorbidities<sup>28</sup>.

In the characterization of the cohort, a low prevalence of chronic diseases was described; this is relevant because chronic-degenerative diseases, such as diabetes, high blood pressure or cardiovascular or pulmonary diseases are recognized as important risk factors for hospital mortality in the age groups of 30 to 50 years when combined with obesity and smoking<sup>29</sup>. Participants had an average age of 40 years. The risk of developing a serious infection in men after 40 years old is higher compared to the 0- to 39-year-old group. In the 40-59 age range, increase by approximately 4% of the overall total, while in the over-60 category the total number of deaths amounts to about 92% of all deaths recorded in both men and women<sup>30</sup>.

Within the limitations of the study, we identified that a large part of the follow-up took place in the period between the second and third waves of COVID-19 cases, which could interfere with the incidence of cases in health personnel. The present study

has naturally assigned groups, so there is no control of the intervening variables. Also, the tracing of incident cases of SARS-CoV-2 was carried out historically through routine passive surveillance, which limits the detection of confirmed cases, mainly asymptomatic cases. Artificial immunization alone has proven to be effective against the disease, so it is suggested to evaluate the impact that this protection could generate in the general population.

It could not be established that the observed reduction in cases was due to the history of infection with a complete immunization schedule due to the lower proportion of cases presented and it will be important to continue long-term follow-up to validate whether this reduction is attributable to hybrid immunization and whether it will provide protection against new variants<sup>31</sup>. It is necessary that the evaluation of the efficacy of vaccines considers a wide range of confounding factors in systematic sampling and those generated in epidemiological surveillance to improve the interpretation of the results<sup>8</sup>, and that subsequent studies establish other aspects of the social determinants of the individual, the time that elapsed since immunization, the number of doses applied and the measurement of neutralizing antibodies<sup>32</sup>.

## Conclusions

The risk of SARS-CoV-2 infection is low in the first six months after completing a vaccination schedule regardless of COVID-19 history. Hybrid immunization could contribute to reducing the risk of SARS-CoV-2 infection in health personnel, enhancing the immunity generated by immunization against COVID-19. The history of primary infection by SARS-CoV-2 was proportionally more present in male health personnel and with an average age of 40 years.

## Funding

The authors declare there are no sources of funding .

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