COVID-19 Immunity in the Cohort of IRCCS San Raffaele Hospital Employees after BNT162b2 Vaccination: A Retrospective Observational Study

Immunità da Covid-19 nella coorte di dipendenti dell'IRCCS Ospedale San Raffaele dopo Vaccinazione BNT162b2: Uno Studio Osservazionale Retrospettivo

Keywords: Health personnel; COVID-19; BNT162b2 Vaccination; Pandemic; Hospital Employees; Cohort Study; Occupational Disease; Preventive Medicine

Parole Chiave: Personale Sanitario; COVID-19; Vaccinazione BNT162b2; Pandemia; Dipendenti Ospedalieri; Studio di Coorte; Medicina Occupazionale; Medicina Preventiva

Abstract

Introduction. The Coronavirus Disease-2019 (Covid-19) pandemic represents the most severe health and socioeconomic crisis of our century. It began with the first reports in China, in the Wuhan region in December 2019, and quickly spread worldwide, causing a new Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-CoV-2). Among the population most at risk of infection and developing severe forms of the disease are the elderly and healthcare workers, who are more exposed to infected individuals. On December 11, 2020, the Food and Drug Administration approved the emergency use of the BNT162b2 vaccine, the first mRNA vaccine in history. Since then, the total number of vaccine doses administered has exceeded 12 billion. Italy was the first European country to be hit by the pandemic, recording the highest number of total Sars-Cov-2 cases (25,695,311) and, after the first 70 days, had the highest crude mortality rate (141.0 per 100,000). In this study, we analyze the rate of Covid-19 infection among healthcare workers at the San Raffaele Scientific Institute in Milan before and after receiving the BNT162b2 vaccine.
Study design. Retrospective observational cohort study.
Methods. The study analyzed the immunization status of 858 employees of the San Raffaele Scientific Institute in Milan, including doctors, healthcare workers, and administrative staff. The analysis is based on previous studies on the same cohort and is integrated with extrapolation and additional analysis of data from the Preventive Medicine Service's Biobank dataset of the same hospital to estimate the infection rate, duration of the disease, and antibody levels recorded in the personnel before and after receiving the double BNT162b2 vaccination.
Results. The analysis confirms the positive impact achieved by the introduction of mRNA vaccination in reducing the Covid-19 infection rate and increasing antibody levels in healthcare workers. Although the BNT162b2 vaccination may not provide complete protection against Sars-CoV-2, it appears to be able to reduce the number of infections, particularly the more severe and symptomatic forms often detected in individuals with various risk factors and comorbidities, making them more vulnerable. Healthcare workers, who have extensive contact with patients and record the greatest decrease in infection rates, are the population that receives the most benefit from vaccination.
Conclusions. The evidence suggests that vaccinations are essential in protecting high-risk groups, such as healthcare workers, from Covid-19 infection. Providing adequate vaccination coverage to healthcare workers limits infections and decreases the severity of disease manifestations, while also reducing their duration.

Riassunto

Introduzione. La pandemia da Coronavirus Disease-2019 (Covid-19) rappresenta la più grave crisi sanitaria e socioeconomica del nostro secolo. È iniziata con le prime segnalazioni in Cina, nella regione di Wuhan nel dicembre 2019, per poi diffondersi rapidamente in tutto il mondo, provocando una nuova Sindrome da Malattia Respiratoria Acuta Grave Coronavirus 2 (Sars-CoV-2). Tra la popolazione più a rischio di infezione e di sviluppo di forme gravi della malattia vi sono gli anziani e gli operatori sanitari, che sono più esposti ai soggetti infetti. L'11 dicembre 2020 la Food and Drug Administration ha approvato in emergenza l'uso del vaccino BNT162b2, il primo vaccino a mRNA della storia. Da allora il numero totale di dosi di vaccino somministrate ha superato i 12 miliardi. L'Italia è stato il primo Paese europeo ad essere colpito dalla pandemia, registrando il maggior numero di casi totali di Sars-Cov-2 (25.695.311) e, dopo i primi 70 giorni, ha avuto il tasso grezzo di mortalità più alto (141,0 per 100.000). In questo lavoro, analizziamo il tasso di infezione

da Covid-19 nei dipendenti ospedalieri dell'Istituto di Ricovero e Cura a Carattere Scientifico Ospedale San Raffaele prima e dopo aver ricevuto il vaccino BNT162b2.

Disegno dello studio. Studio osservazionale di coorte retrospettivo.

Metodi. Lo studio ha analizzato lo stato di immunizzazione di 858 dipendenti dell'Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele di Milano, tra medici, operatori sanitari e personale amministrativo. È basato sulle analisi condotte nel precedente studio relativo alla stessa coorte, integrandole con l'estrapolazione e l'analisi aggiuntiva dei dati provenienti dal dataset della Biobanca del Servizio di Medicina Preventiva dello stesso ospedale per stimare il tasso di infezione, la durata della malattia e i livelli anticorpali registrati nel personale prima e dopo la doppia vaccinazione BNT162b2.

Risultati. L'analisi conferma l'impatto positivo ottenuto dall'introduzione della vaccinazione con mRNA nel ridurre i tassi di infezione da Covid-19 e nell'aumentare i livelli di anticorpi negli operatori sanitari. Sebbene la vaccinazione BNT162b2 possa non fornire una protezione completa da Sars-CoV-2, sembra in grado di ridurre il numero di infezioni, in particolare le forme più gravi e sintomatiche, spesso rilevate in soggetti con diversi fattori di rischio e comorbilità, e per questo più fragili. Gli operatori sanitari, dato il loro ampio contatto con i pazienti, sono la popolazione che trae maggiori benefici dalla vaccinazione, ottenendo il maggior calo nel tasso di infezione.

Conclusioni. I risultati dello studio rafforzano il ruolo cruciale delle vaccinazioni nella protezione dei gruppi a più alto rischio di infezione da Covid-19 da, come quello degli operatori sanitari. Fornire un'adeguata copertura vaccinale agli operatori sanitari limita le infezioni e le manifestazioni più gravi di malattia, riducendone al tempo stesso la durata.

Main text

Introduction

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 infection as a pandemic (1). Italy was among the first countries in the European region to experience the detrimental effects of the pandemic, partly due to its high proportion of people aged 70 years or older (2, 3). Lombardy region reported the highest crude COVID-19 mortality rate (141.0 per 100,000) 70 days after the beginning of the epidemic, out of all European metropolitan areas with similar socio-demographic characteristics (4, 5).

This situation led the Italian government to promptly implement public health measures, such as limiting travel and avoiding behaviors at risk of encouraging the transmission of the infection (6). The efficacy of implementing fundamental public health principles such as personal hygiene, the utilization of personal protective equipment, was reestablished (7). Italy also adopted rapid antigen tests, which were quickly implemented and regulated in sectors like healthcare and education, where the patient facing staff personnel were at higher risk of infection (8). Healthcare personnel have been at the forefront of the battle against COVID-19, facing an elevated risk of infection due to their continuous exposure to infected patients and colleagues (9-11). To protect these essential workers and ensure the uninterrupted delivery of healthcare services, mRNA-based vaccines for COVID-19 were introduced globally from late 2020 (12).

On 22 December 2020, the Italian Medicines Agency (AIFA) authorizes the marketing of the new anti-COVID-19 vaccine from Pfizer/BioNTech, BNT162b2 in Italy for all those aged 16 or over (13-15). The primary aim of vaccination has been to reduce the risk of infection and reduce the severity of symptoms in case of positive swab tests (16).

This study builds on the previous longitudinal observational study conducted by the Internal Medicine Operating Unit at San Raffaele Scientific Institute in Milan, which assessed the kinetics of immune response of B and T cells using serological tests and ELISpot IFN-γ in healthcare workers and non-healthcare personnel. Demographic and clinical data were collected through an anonymous survey (17, 18).

The San Raffaele Scientific Institute can be considered a particularly relevant center for selecting the study population, due to the following reasons. The Hospital is located in the geographical area where the first two European outbreaks of COVID-19 were found (19). The first case in the metropolitan city of Milan was diagnosed at the San Raffaele Scientific Institute (20). The large tertiary hospital allows to include a substantial sample size. The laboratory and epidemiological data collected during the epidemic (also with the collaboration of members of the CORONADX research group) were deemed sufficiently complete.

The aim of the study was to evaluate the impact of mRNA vaccination on COVID-19 infection rates, antibody levels and duration of illness among employees of the San Raffaele Scientific Institute.
Specific objectives were to determine the incidence of COVID-19 infections among healthcare workers using PCR swabs (both before the first dose of mRNA vaccine and up to 10 months after vaccination), to evaluate the antibody levels of individual employees, with particular attention to IgM and IgG values, before the first vaccination and at 10-month intervals after the first, second and third dose (booster), the determination of the COVID-19 disease average duration in workers with at least one mRNA vaccination, considering the time elapsed between the day of onset of the disease and the day of return to work, and the determine changes in Covid-19 symptoms, in relation to comorbidities and pre-existing risk factors, in infections that occurred before and after vaccination with BNT162b2.

Methods

This retrospective cohort study included 856 employees of the San Raffaele Scientific Institute in Milan, encompassing patient-facing staff, such as doctors and other healthcare professionals, and non-patient-facing administrative staff. Inclusion criteria were age 18 years or older and having received at least one dose of the BNT162b2 mRNA COVID-19 vaccine from January to June 2021 and up to a maximum of three doses, limited to the time period considered from the administration of the questionnaires by the Internal Medicine Operating Unit 10 months after the first dose.
The data are extrapolated from the anonymized database of the Internal Medicine Operating Unit, containing information on sex, age, profession, anthropometric measurements, medical history, drug therapy and symptoms in case of infection or post-vaccination. This data was collected through questionnaires administered to HSR employees, 6 months after vaccination. The survey aimed to collect demographic and anthropometric data, as well as medical history and adverse effects following the administration of two doses of the vaccine. Data on pre-existing comorbidities were collected, classified as follows: (a) current or previous cancer; (b) allergic conditions; (c) diabetes mellitus (type 1 or type 2); d) blood diseases (anaemia, coagulopathies); (e) history of immunosuppression/transplants; f) cardiovascular diseases; g) neurological conditions; h) autoimmune diseases; i) infectious diseases; (l) history of smoking; (m) pharmacological treatment; The questionnaire also included information on medical events related to COVID-19, with a focus on COVID-19 viral infections contracted less than or more than 6 months before vaccination. COVID-19 symptoms were studied through a series of questions, covering various symptoms and effects. Questions about vaccination side effects included localized reactions (pain, swelling, redness at the injection site), systemic reactions (fever, fatigue/malaise, chills, headache, vomiting/nausea, diarrhea, muscle pain, swollen lymph nodes, dizziness /confusion), allergic reactions (widespread itching, rash unrelated to the injection, asthma, throat tightness, anaphylaxis) and other reactions (altered sleep quality, memory loss, anxiety, psychological distress, feelings of gratitude/relief/ joy, attention deficit, palpitations, pain, loss of appetite, increased thirst, intolerance to heat/cold, menstrual cycle disorders, difficulty carrying out daily activities). Finally, employees were asked to identify themselves as either patient-facing staff (physicians, nurses, physiotherapists, psychologists, social health workers, technical assistance workers, technical assistance workers, speech therapists, obstetricians, orthoptics), or nonpatient-facing staff (Administrative Employees).
This first dataset was integrated with the data contained in a second anonymized Database of the Hospital Biobank, created on the basis of the analyzes carried out by the Preventive Medicine Service on the disease status of HSR employees. All data was collected over time after anonymization. Health checks and employee health surveys have evolved over time. In October 2020, only RT-PCR was being performed. From November 2020 to January 2022, RT-PCR was used for the diagnosis of symptoms compatible with Covid, and upon return to hospital activity after Covid infection/quarantine due to close contact, as well as upon return from abroad, and upon return after illness with symptoms compatible with Covid in subjects negative to the swab carried out at the onset of symptoms, and as screening of contacts in healthcare workers. A second type of test using Rapid Antigenic was carried out as screening for access to the departments.
Since January 2022 the procedures have been updated again and RT-PCR was only necessary for the diagnosis of symptoms compatible with Covid, while Rapid Antigen was used in case of return to hospital activity after illness/quarantine, and screening of close contacts in healthcare workers.
A maximum of 3 doses of BNT162b2 vaccine are taken into consideration in the study, as they fall within the complete cycle as per decree No. 172/2021. La dose booster was intended for the prevention of SARS COV 2 infection and made mandatory from 15 December 2021, at least 5 months after the administration of the second dose, for all categories of workers at greater infectious risk, such as healthcare workers, and also extended to non patient-facing staff.
Antibody titers were tested by the Elecsys Anti-SARS-CoV-2 assay (Roche, Basel, Switzerland) specific for the viral SARS-CoV-2 1 Nucleocapsid protein (N) at T0 and by the Elecsys SARS-CoV-2-S (Roche, Basel, Switzerland) against the RBD of the viral Spike (S) protein at T1, T2, T3, and T4. The Roche Elecsys Anti-SARS-CoV-2 is an electrochemiluminescence immunoassay (ECLIA) targeted on total immunoglobulins (IgTot: IgA, IgG, and IgM) against the N-protein. The result is given as a cut-off index (COI) and qualitative results: for COI 1.0, the sample is reactive and positive (manufacture datasheet: 09289267501V0.6). The manufacturer indicated a specificity of 99.80% and a sensitivity of 99.50% 14 days post-PCR confirmation. The Roche anti-SARS-CoV-2-S is an ECLIA detecting total immunoglobulins (IgTot: IgA, IgG, and IgM) against the RBD of the viral S-protein. The quantification range is between 0.4 and 250.0

U/mL, which is further extended to 2500.0 U/mL by a 1:10 dilution of the sample automatically performed by the instrument. Specificity and sensitivity (≥ 14 days after diagnosis) are 174 99.98% and 98.8%, respectively, when the manufacturer's suggested COI for positivity 0.8 U/mL is 175 used (21).

Peripheral blood samples were collected at five crucial time points. T0, the Day 0 shortly before the first vaccine administration. T1, 21 days after the first dose (shortly before the second dose) to assess the response to the initial vaccination. T2, 21 days after the second dose, reflecting the immune response upon completing the vaccination regimen. T3, 6 months after the first dose. T4, Prior to the booster dose (10 months after the first dose).

Results

	Total	**Females**	**Males**
HSR Employees	856	553 (64.60%)	303 (35.40%)
AGE (years), median (IQR)	53.75 (25.17-79.01)	52.69 (25.17-78.86)	56.06 (26.04-79.01)
BMI (kg/m²), median (IQR)	23.60 (12.21-44.27)	22.32 (12.21-44.27)	25.26 (12.21-44.27)
PRE-VACCINE INFECTIONS			
OCCUPATION		INFECTED	NOT INFECTED
	PATIENT FACING STAFF	51 (9.19%)	504 (90.81)
	DOCTORS	17 (6.61%)	242 (93.39%)
	HEALTH CARE PROFESSIONS*	34 (11.49%)	262 (88.51%)
	NON PATIENT FACING STAFF	15 (14.85%)	286 (85.15%)
POST-VACCINE INFECTIONS			
OCCUPATION		INFECTED	NOT INFECTED
	PATIENT FACING STAFF	23 (4.0%)	532 (96%)
	DOCTORS	7 (2.70%)	252 (97.28%)
	HEALTH CARE PROFESSIONS*	16 (5.40%)	280 (94.6%)
	NON PATIENT FACING STAFF	16 (5.31%)	285 (94,69%)

(*): The group includes Nurses, OSS, OTA, Psychologists, Physiotherapist, Obstetrics, Oral Hygienist and Ortoptics
Tab. 1: Characteristics of the study sample

Comorbidities	**HSR Employeers with Comorbidities (%)**

Current Neoplastic Disease or Under Treatment in the previous year	14 (1.63%)
Respiratory Pathology	40 (4.67%)
Obesity (BMI>30)	41 (4.79%)
Cardiovascular Disease	38 (4.44%)
Neurological Disease	20 (2.33%)
Diabetes Mellitus	16 (1.87%)
Chronic Renal Failure	5 (0.58%)
Coagulopathies	8 (0.93%)
History of Immunosuppression/Organ Transplant	8 (0.93%)
Hypertension	161 (18.81%)
Liver Disease	3 (0.35%)
Sickle Cell Anemia or Thalassemia	6 (0.70%)
Autoimmune Disease	71 (8.29%)
Gastrointestinal Disease	17 (1.96%)
Infectious Disease	6 (0.70%)
Previous Smoking Hstory	92 (10.75%)
Current Smoking History	99 (11.57%)

Tab. 2: Characteristics of Comorbidities in HSR Employees

Symptoms	Pre-Vaccine Covid-Infected HSR Employees (%)	Post-Vaccine Covid-Infected HSR Employees (%)
Fever ≥ 37.5 °C & Chills	25 (2.91%)	2 (0.23%)
Cough	11 (1.28%)	1 (0.12%)
SoreThroat	18 (2.10%)	2 (0.23%)
Rhinorrea	12 (1.40%)	4 (0.46%)
Dyspnea	9 (1.05%)	0 (0.0%)
Chest Pain	5 (0.58%)	1 (0.12%)
Anosmia/Ageusia	15 (1.75%)	6 (0.70%)
Myalgia/Arthralgia	15 (1.75%)	1 (0.12%)
Asthenia	27 (3.15%)	3 (0.35%)
Headache	17 (1.98%)	5 (0.58%)
Nausea/Vomiting	7 (0.82%)	7 (0.82%)
Diarrhea/Abdominal Pain	4 (0.47%)	4 (0.47%)
Conjunctivits	6 (0.70%)	3 (0.35%)

Tab. 3: Symptoms Distribution in Covid-Infected HSR Employees

The study highlighted a reduction in the incidence of COVID-19 infections in the different categories of workers at the San Raffaele Hospital, following vaccination with mRNA. Out of a total of 858 healthcare workers, incident Covid Infections affected 7.7% (66) HSR Employees pre-BNT162b2 vaccination, while post-BNT162b2 vaccination this dropped to 4.6% (39) (Fig. 1.A).

Incidence Covid infections by gender affected 7.6% and 7.8% of men and women pre-vaccination respectively, decreasing to 4% and 4.9% in the post-Vaccination phase. (Fig. 1.B).

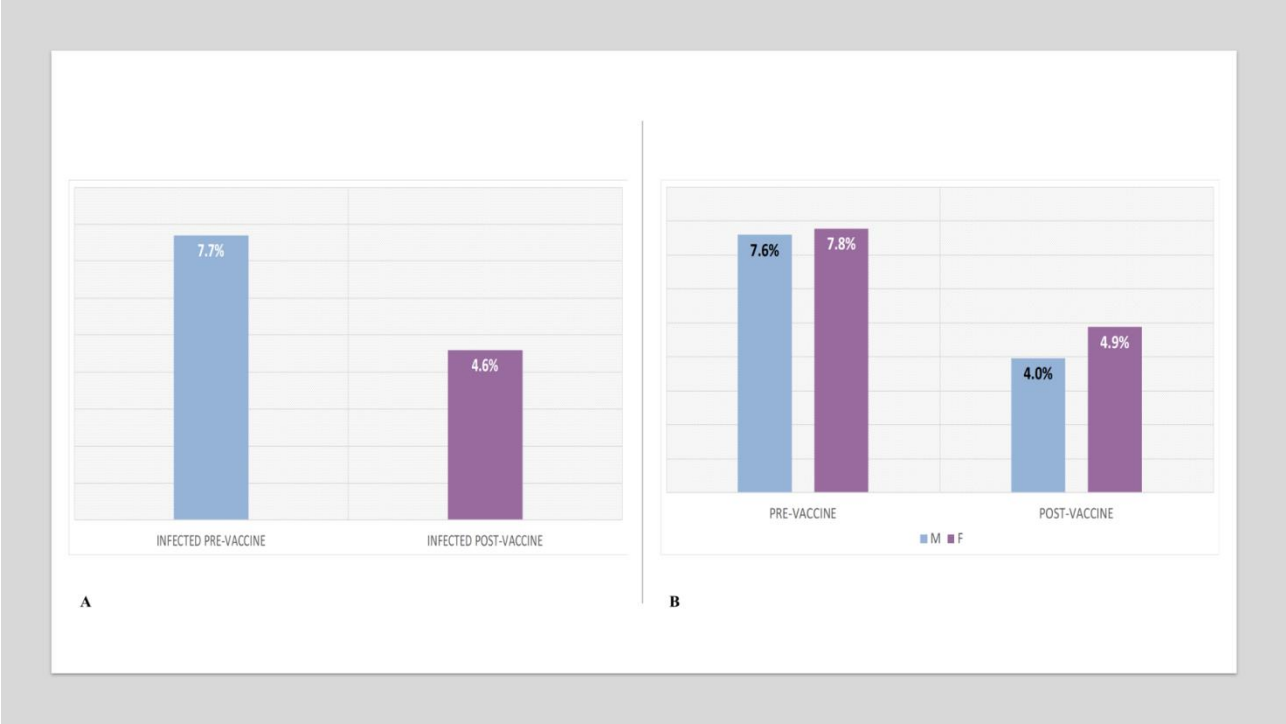


Figure 1.A; Incidence of Coronavirus Infections in HSR Employees pre-and-post BNT162b2 vaccination
Figure 1.B; Incidence of Coronavirus Infections by gender in HSR Employees pre-and-post BNT162b2 vaccination

The study recorded a drop in the infection rate from 9.2% to 4.1% (from 51 to 23 employees) for patient-facing staff with patients. On the contrary, among staff not in contact with the patient, a stable number of infections remained in the two phases, affecting 5 and 5.3% of employees (from 15 to 16 employees) (Fig. 2.A).
A decrease in the number of Covid infections was observed in medical personnel from 3.1% to 2.7% (from 17 to 7 employees), but even more significant in healthcare workers in strict contact with patients (Nurses, Social-Health Operators(OSS), Technical-Assistance Operators(OTA), Psychologists, Physiotherapists, Obstetricians, Orthoptics) 11.5% to 5.4% (34 to 16 employees) (Fig. 2.B).

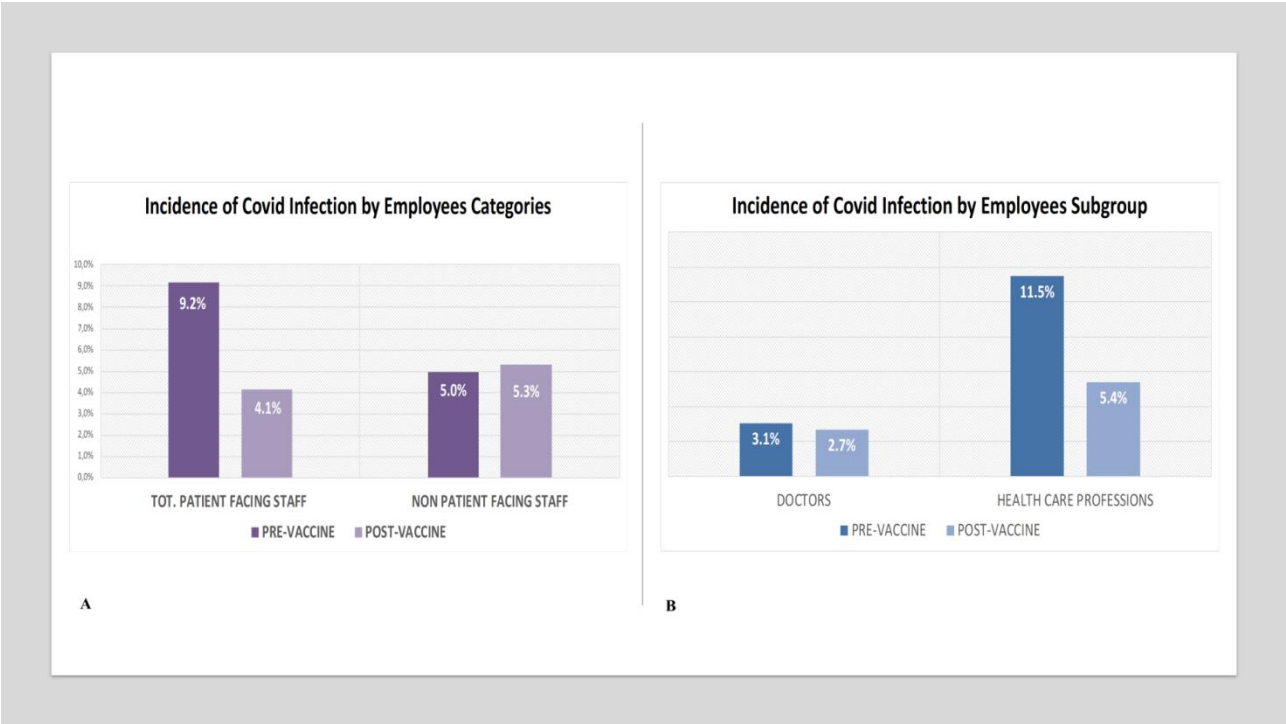


Figure 2.A; Incidence of Coronavirus Infections by HSR Employees Categories pre-and-post BNT162b2 Vaccination
Figure 2.B; Incidence of Coronavirus Infections by HSR Employees Subgroup pre-and-post BNT162b2 Vaccination

The incidence of Covid-19 infections was then analyzed, before and after vaccination, in subgroups of workers, divided on the basis of the number of pre-existing risk factors: workers who did not present comorbidities, employees who had at least one, those with 2 or more comorbidities. The analysis shows a significant decrease in the incidence of post-vaccination infections in each group of patients. In the group without comorbidities, the incidence dropped from 9.3% to 4.8%. In the second group, workers with at least one comorbidity, showed a decrease from 6.9% to 4.3%. Even in the third group, among the most vulnerable workers, there is a drop, albeit more modest, from 5.3% to 4.6% (Fig. 3).

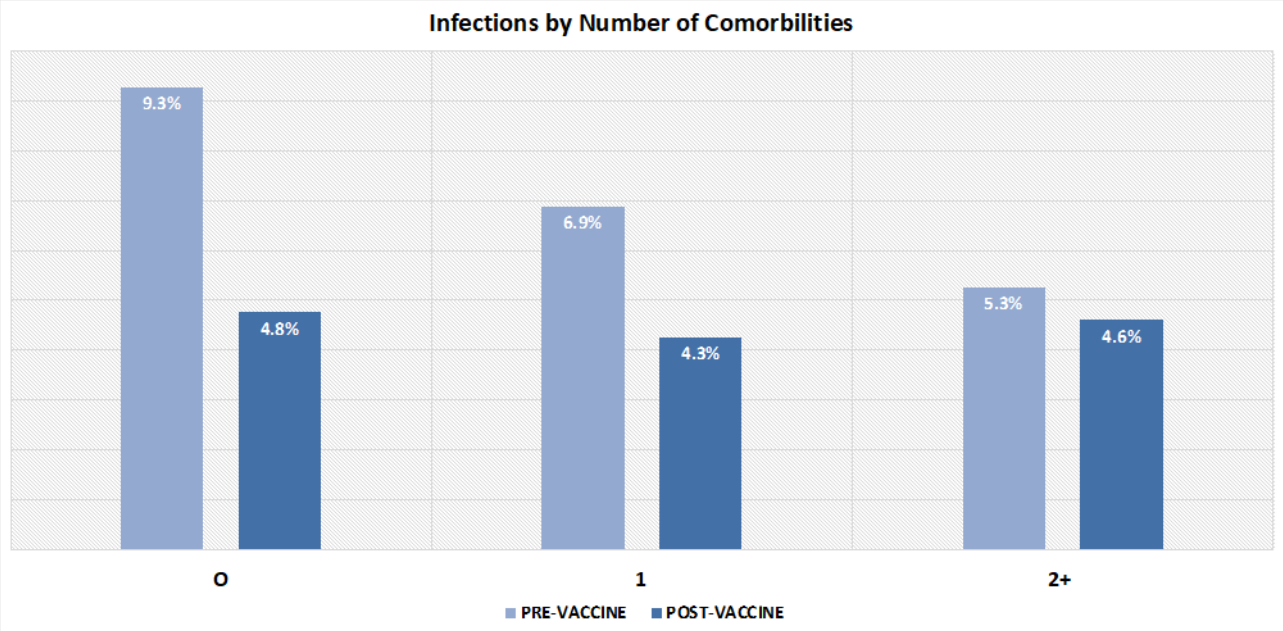


Figure 3: Incidence of Coronavirus infections in HSR Employees by number of comorbidities pre-and-post BNT162b2 Vaccination

From the analysis of health coverage offered through BNT162b2 vaccination, in terms of incidence, cases of Covid-19 infection decreased from 66 to 17 after a full course, and the median period of time without infection in vaccinated employees was 47 days (p.max: 93 days. p.min: 5 days) (Fig.4).

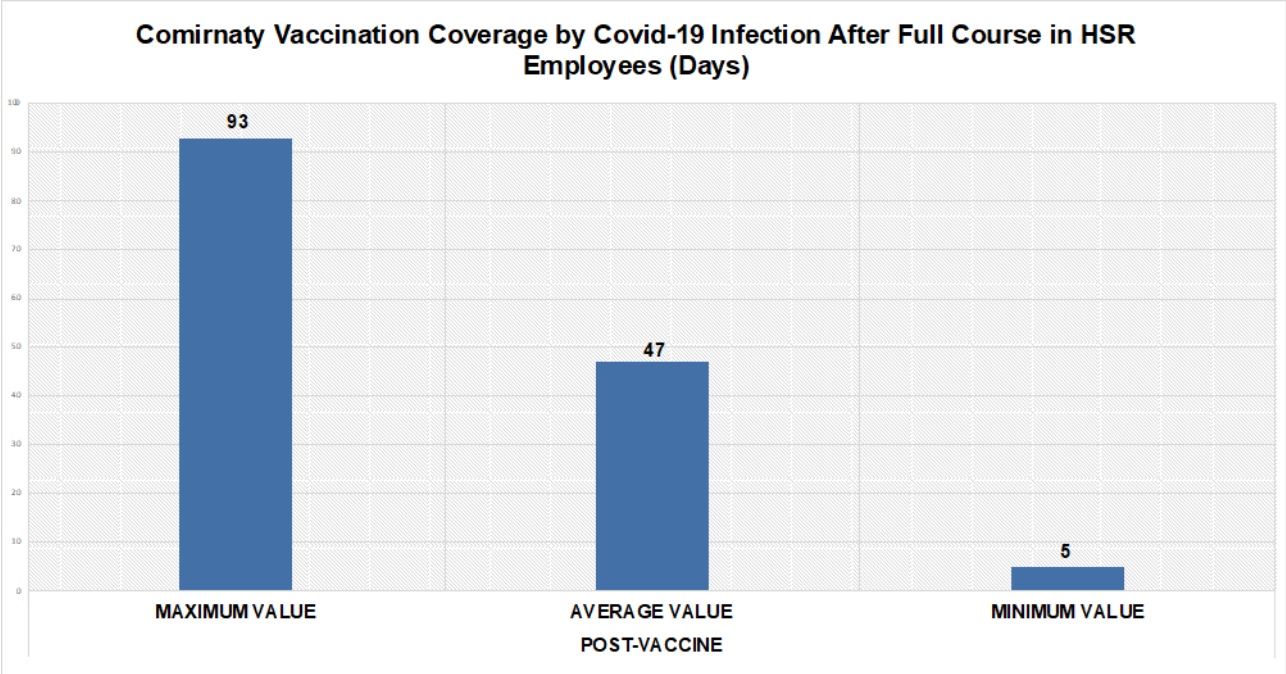


Figure 4: Representation of the Duration of BNT162b2 Vaccination Coverage Before Reinfection in HSR Employees

Among the different forms of Covid-19 infection (asymptomatic, monosymptomatic, polysymptomatic - with two symptoms - and multisymptomatic - with three or more symptoms -), there has been a general decline in the incidence of Covid-19 post-vaccination, with a reduction from 2.7% to 0.7% in the asymptomatic form, from 0.8% to 0.5% in the monosymptomatic form, from 0.8% to 0.1% in the polysymptomatic form, up to a decrease from 3.4% to 0.7% in the multi-symptomatic one (Fig. 5).

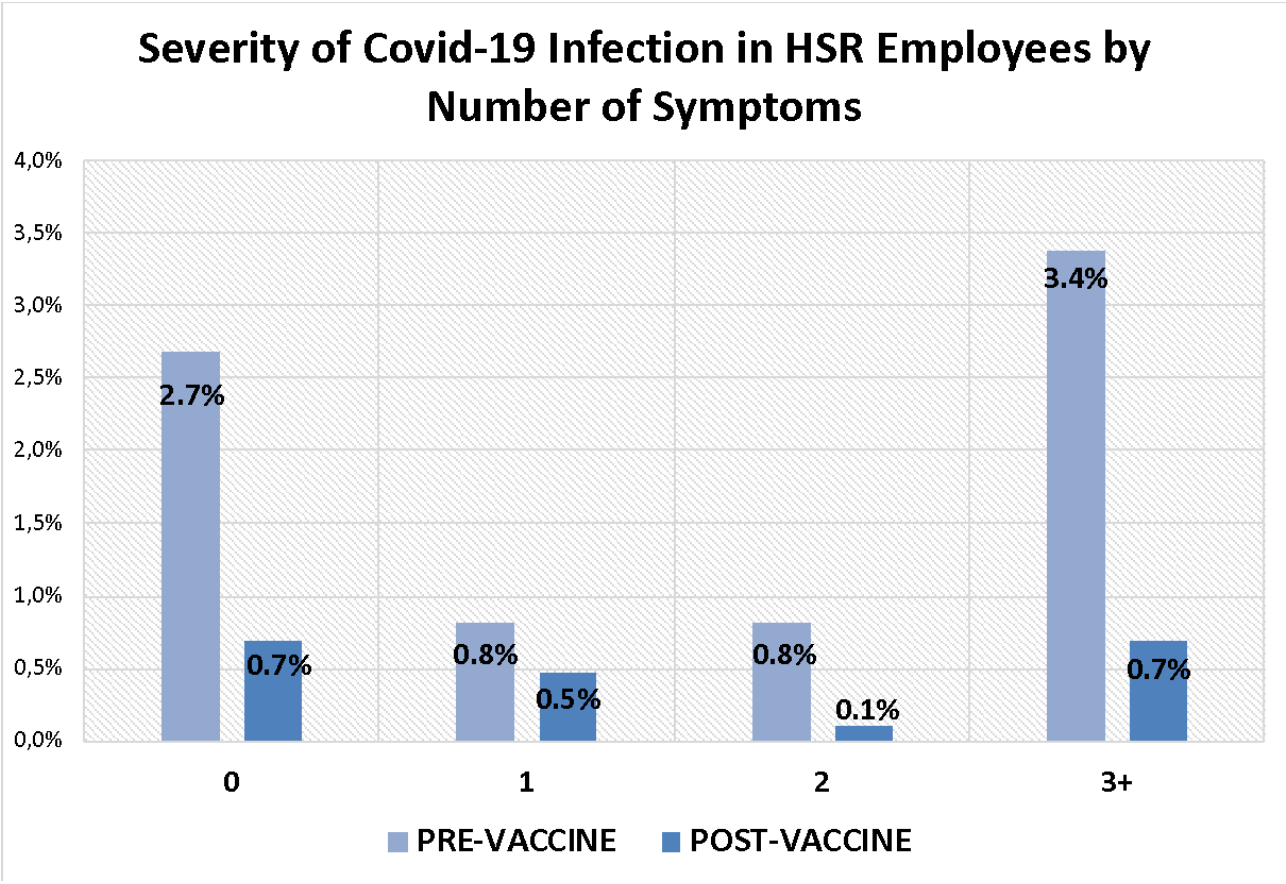
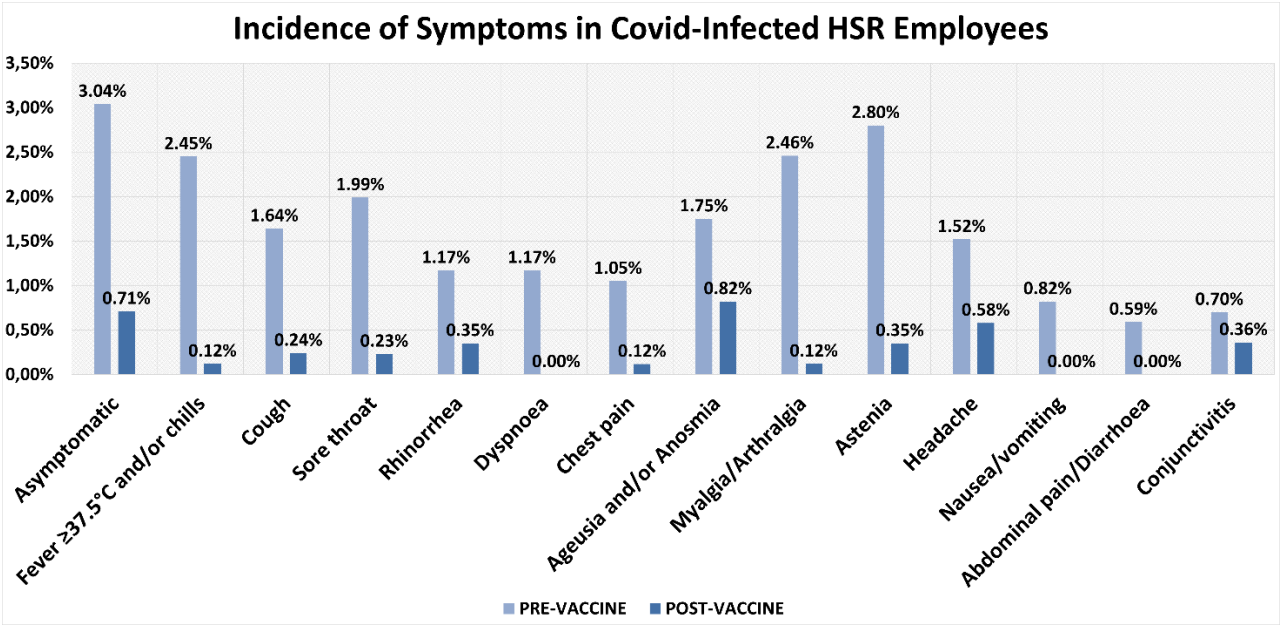
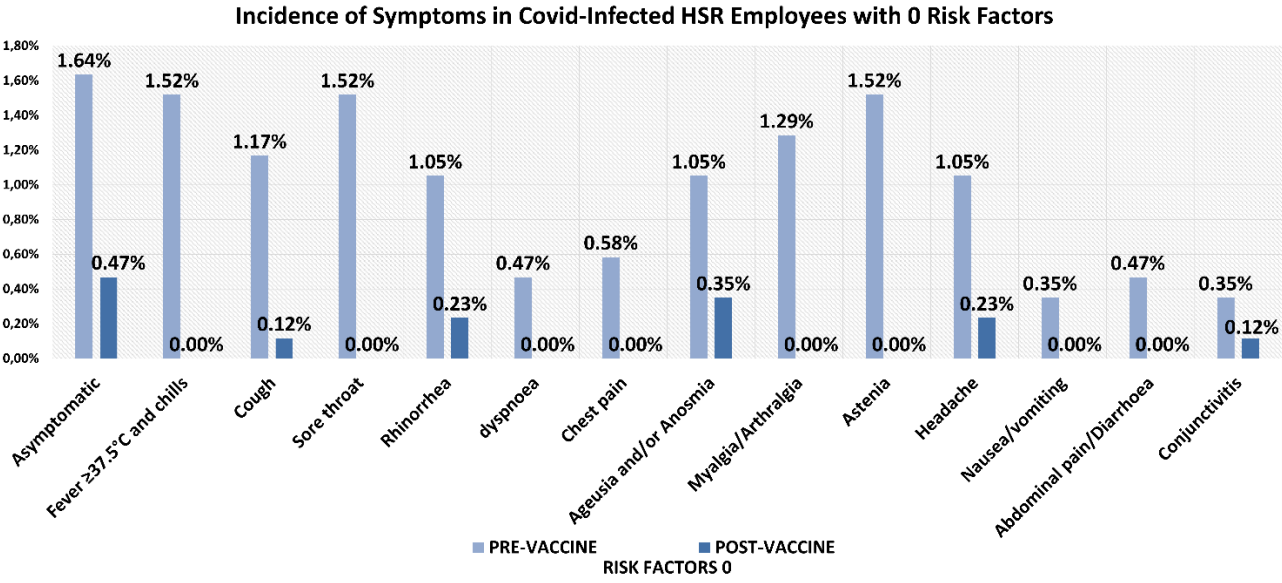


Figure 5: Incidence of different forms of Coronavirus disease (asymptomatic, mono-symptomatic, poly-symptomatic, pluri-symptomatic) in HSR Employees pre-and-post BNT162b2 Vaccination

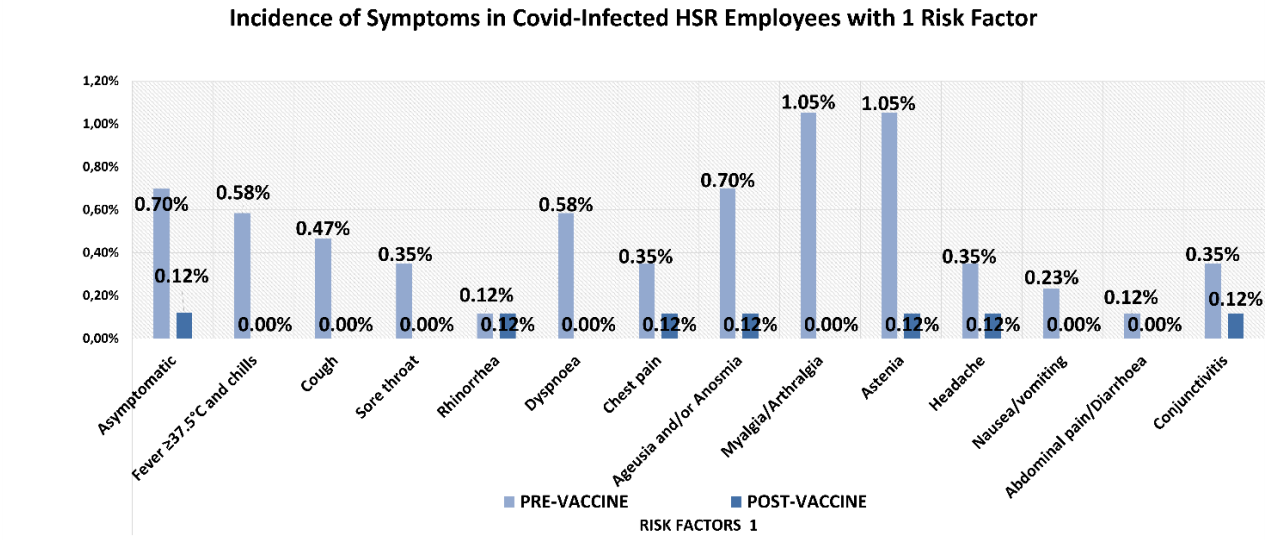
From the analysis of symptoms, a general decline in symptoms is observed in post-vaccination infections.
In the subgroup of employees without risk factors, and in employees with at least one risk factor, they were associated with milder forms with reduction of symptoms, compared to their counterparts before vaccination (Fig.6.B) (Fig.6. C).
However, Covid-19 infection in employees who had 2 or more risk factors remains associated with a more symptomatic condition compared to employees without comorbidities. (Fig.6.D).



6.A



B



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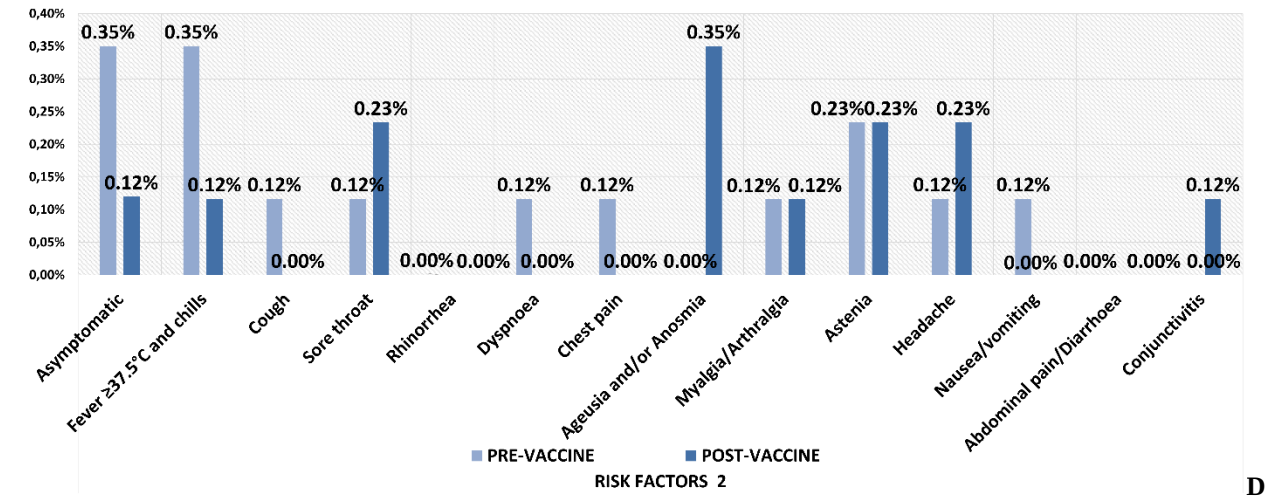


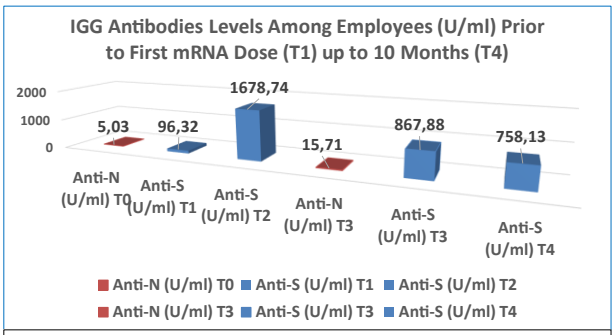
D

Figure 6.A; Incidence of Symptoms in Coronavirus-Infected HSR Employees pre-and-post BNT162b2 vaccination
Figure 6.B; Incidence of Symptoms in Coronavirus-Infected HSR Employees with 0 Comorbidities pre-and-post BNT162b2 vaccination
Figure 6.C; Incidence of Symptoms in Coronavirus-Infected HSR Employees with 1 Comorbidities pre-and-post BNT162b2 vaccination
Figure 6.D; Incidence of Symptoms in Coronavirus-infected HSR Employees with 2 or more Comorbidities pre-and-post BNT162b2 vaccination

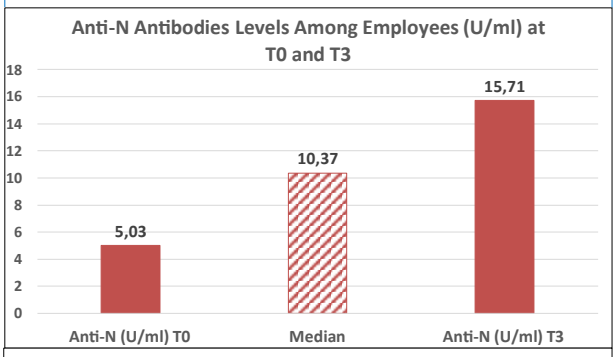
From the analysis of the blood samples, (collected at 5 time points: the day before the first vaccine administration (T0); 21 days after the first dose and shortly before the second dose (T1); 21 days after the second dose (T2), 6 months after first dose (T3), 10 months after first dose (T4)). IgG antibody levels have demonstrated substantial increases after each vaccine dose enhancing immune responses. The antibody median levels found among employees in the different pre- and post-vaccination phases were summarized, specifically reporting the levels of 2 different types of antibodies: Anti-S (Anti-RBD) and Anti-N. (Fig. 7.A).

The population of HSR employees showing an anti-N-specific antibody titer >1 U/ml at baseline (T0) was considered naturally seropositive (with a history of SARS-CoV-2 infection prior to vaccination. Pre-vaccination levels were around 5.03 U/ml, tripled in the pre-booster dose phase, reaching average values of 15.71 U/ml, with a median value 6 months after the first vaccination of 10.37 U /ml. (Fig. 7.B).

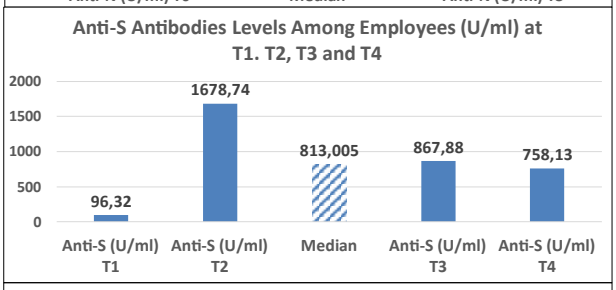
The levels of anti-S antibodies at T1, T2, T3 and T4 showed how a second administration of the mRNA vaccine, added to the first, 21 days later, produced a significant stimulation of the immune system with a significant increase from 96.32 to 1678.74 U/ ml. While after 6 months a halving of the antibody values was observed, reaching a value of 867.88 U/ml, further decreased in T4, 758.13 U/ml (Fig. 7.C-E).


IGG Antibodies Levels Among Employees (U/ml) Prior to First mRNA Dose (T1) up to 10 Months (T4)
2000
1000
0
5,03
96,32
1678,74
15,71
867,88
758,13
Anti-N (U/ml) T0
Anti-S (U/ml) T1
Anti-S (U/ml) T2
Anti-N (U/ml) T3
Anti-S (U/ml) T3
Anti-S (U/ml) T4
Anti-N (U/ml) T0
Anti-S (U/ml) T1
Anti-S (U/ml) T2
Anti-N (U/ml) T3
Anti-S (U/ml) T3
Anti-S (U/ml) T4

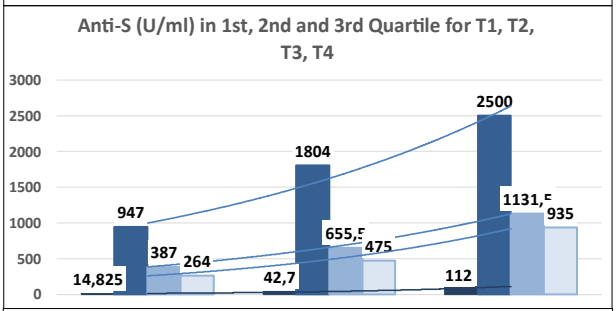
A


Anti-N Antibodies Levels Among Employees (U/ml) at T0 and T3
18
16
14
12
10
8
6
4
2
0
5,03
10,37
15,71
Anti-N (U/ml) T0
Median
Anti-N (U/ml) T3

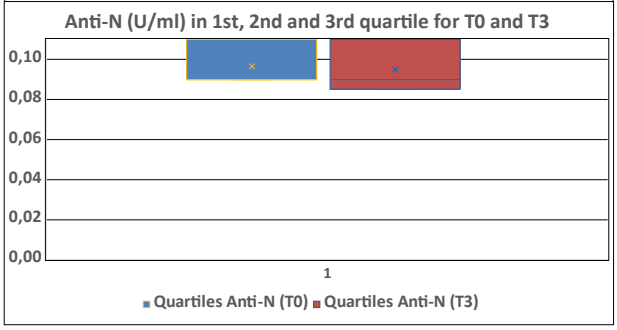
B


Anti-S Antibodies Levels Among Employees (U/ml) at T1. T2, T3 and T4
2000
1500
1000
500
0
96,32
1678,74
813,005
867,88
758,13
Anti-S (U/ml) T1
Anti-S (U/ml) T2
Median
Anti-S (U/ml) T3
Anti-S (U/ml) T4

C


Anti-S (U/ml) in 1st, 2nd and 3rd Quartile for T1, T2, T3, T4
3000
2500
2000
1500
1000
500
0
947
387
264
14,825
1804
42,7
655,5
475
2500
112
1131,5
935

D


Anti-N (U/ml) in 1st, 2nd and 3rd quartile for T0 and T3
0,10
0,08
0,06
0,04
0,02
0,00
1
Quartiles Anti-N (T0)
Quartiles Anti-N (T3)

E

Figure 7.A; IgG Antibodies Levels Among Employees (U/ml) prior to First mRNA Dose (T1) up to 10 Months
Figure 7.B; Anti-N Antibodies Levels Among Employees (U/ml) at T0 and T3
Figure 7.C; Anti-S Antibodies Levels Among Employees (U/ml) at T1, T2, T3 and T4
Figure 7.D; Anti-S (U/ml) in 1st, 2nd and 3rd Quartile for T1, T2, T3, T4
Figure 7.E; Anti-N (U/ml) in 1st, 2nd and 3rdQuartile for T0 and T3

A reduction in the days of absence from work due to Covid-19 illness was also ascertained, with an average absence time that dropped from 16.3 days in the 6 months before the first vaccination to 14.25 days in the 10 months after -vaccination (Fig. 8).

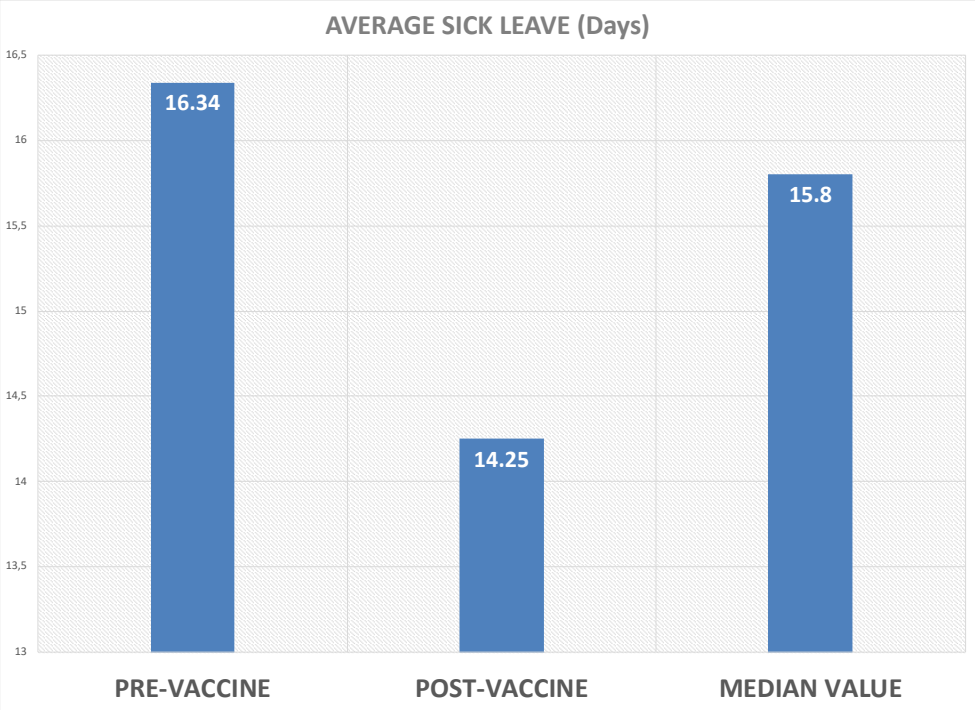


Figure 8; Representation of the Average Sick-Leave (Days) in HSR Employees pre-and-post BNT162b2 Vaccination

Discussion

Our study considered a cohort of 856 employees of the IRCCS San Raffaele Hospital, including both professional figures in close contact with the patient (facing-patient staff) and administrative figures, not in close contact with the patient (nonpatient-facing staff). The common inclusion criteria were age over 18 years and having received at least one dose of the BNT162b2 mRNA COVID-19 vaccine (BNT162b2). The study demonstrates the effectiveness of the BNT162b2 vaccination (VE) and therefore the usefulness and priority of use in one of the professions most at risk of contracting COVID-19 infection, such as the category of Healthcare Workers. From the NEJM clinical trial on which the EMA's evaluation was based, we know that the safety and efficacy of the BNT162b2 vaccine against laboratory-confirmed Sars-CoV-2 infection is equal to 95% (22).
As demonstrated in our study, even among the different categories of workers at San Raffaele Hospital, the incidence of Covid-19 infection in a cohort of 858 HSR employees decreased from 7.7% before vaccination to 4.6%.
Specifically, for the category of patient-facing staff, we recorded a decrease in the infection rate from 9.2% to 4.1%, compared to a more stable rate (from 5% to 5.3%) in the subgroup of administrators who are exposed to a lower risk, as found in the English study (SIREN), Israeli, and Italian studies. However, the greatest effectiveness is observed in the categories of patient-facing staff, and in fact, we found the highest effectiveness after vaccination in the subgroup of healthcare workers (nurses, OSS, OTA, psychologists, physiotherapists, obstetricians) which decreased from 11.5% to 5.4% (from 34 to 16) compared to medical personnel who recorded only a minimal decrease from 3.1% to 2.7% (from 17 to 7 employees) (23-25).
From the analysis of this German article, as well as this second publication from the United Kingdom, a link is shown between pre-existing comorbidities and more severe manifestations of Covid-19, which may lead to a higher likelihood

of hospitalization within 90 days. In both cases, vaccination provides greater protection for the most at-risk personnel, resulting in a general decrease in infections and limiting the occurrence of severe forms of the disease. Additionally, our subdivision of HSR personnel based on the number of comorbidities reveals a general decreasing trend in infections and subsequent development of illness and serious complications, with a reduction of 4.5% in the group without comorbidities and a more modest reduction of 0.7% in the most vulnerable patients (26, 27).
Furthermore, the BNT162b2 vaccine does not guarantee complete protection against Sars-Cov-2 infection, and this study also demonstrates the possibility of becoming infected after one or both doses of BNT162b2. Our study identifies cases of infection occurring a few days after the second dose (as early as 5 days) and even after reaching the maximum efficacy of 95% coverage 7 days after the second dose (28-30).
From our analysis of Covid-19 infection symptoms, we have observed a clear and overall decrease in symptoms in post-vaccination cases. However, it is important to note that Covid-19 infections with two or more risk factors remains associated with a more symptomatic disease, which can worsen already complex conditions, highlighting greater fragility and propensity for more clinically serious diseases in this category. As known in the literature, those who experienced symptoms were more likely to report adverse events. Vaccination is highly recommended for the most vulnerable individuals, as it helps reduce the incidence of severe forms and provides better protection for those with complicated medical histories, resulting in a general reduction in symptoms (31-35).
The results overall highlight the benefits of mRNA vaccination in mitigating the risk of COVID-19 infection among healthcare workers.
The kinetics of antibodies show that a single dose following an infection leads to a greater production of immunoglobulins compared to two doses of BNT162b2 given 3 weeks apart (36-38). The robust antibody responses observed after vaccination suggest increased protection against the virus, which is critical for maintaining a safe and uninterrupted healthcare environment.
Antibody titers increase rapidly after the first dose and remain more stable over time, especially in HIV-positive subjects. On the other hand, antibody titers in individuals who have never been infected show a gradual growth that increases exponentially after the second dose. Both groups, as demonstrated in the literature, experienced a decrease in Ig levels already 6 months after completing vaccination (39-42).
From a health surveillance perspective, it would be interesting to be able to investigate the effectiveness of a new vaccination cycle with booster doses in the population of HSR employees. The systematic collection of data relating to adverse effects and local resilience would in fact benefit from the specific skills of the population under study and would thus contribute to monitoring the safety of Covid-19 vaccines(43).

Conclusions

This cohort study conducted at the IRCCS San Raffaele Hospital in Milan confirms the positive impact obtained from the introduction of mRNA vaccination on reducing COVID-19 infection rates and increasing antibody levels in the healthcare worker population. In particular, the effectiveness of mRNA vaccination in reducing severe forms of Covid infection is demonstrated, as is the poor ability to prevent reinfections, also given the high rate of SARS-CoV-2 variants. Exposure to patients proves to be an important risk factor for Covid-19 infection, so the population of healthcare workers turns out to be a population at greater risk of infection than the general population. Healthcare workers (nurses, social health workers, etc.) benefit most from mRNA vaccination, with a greater reduction in the infection rate after vaccination. Furthermore, the presence of comorbidities in the population infected with Covid-19 is associated with more symptomatic forms of the disease. These findings highlight the critical role of vaccination in offering adequate coverage to healthcare workers and limiting disruptions in healthcare delivery during the pandemic.

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