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SARS-CoV-2 infection: efficacy of extensive vaccination of the healthcare workforce in a large Italian hospital

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Abstract

Background: *A prospective observational study involved 13,787 Health Care Workers (HCWs) of a large hospital to assess the effectiveness of a SARS-CoV-2 mRNA vaccine.* **Methods:** *The daily incidence of infections was estimated from 1st October 2020 to 30th April 2021 and compared with that of the province of Turin (2.26 million). In the middle of this period, a mass vaccination began among HCW, and its effect was assessed.* **Results:** *In the first half-period, 1,163 positive HCWs were observed, the average daily incidence rate per 100,000 being 79.58 (± 15.58; 95% CI) compared to 38.54 (± 5.96; 95% CI) in the general population (p<0.001). The vaccination campaign immunized 9,843 HCWs; among them, the average daily incidence was 14.23 (± 2.73; 95% CI) compared to 34.2 (± 2.95; 95% CI) in the province (p<0.001). Among fully vaccinated HCW, 59 cases were observed, giving rise to an incidence of 6.3 (± 2.66; 95% CI) much lower than in the province (p<0.001). In the second half of the observation period, the RR for HCWs compared to the province dropped from 2.07 (1.96 – 2.18; 95% CI; p<0.001) to 0.5 (0.42 – 0.58; 95% CI; p<0.001) and to 0.17 (0.13 – 0.22; 95% CI; p<0.001) for unvaccinated and vaccinated HCWs, respectively. The RR of vaccinate HCW was 0.43 (0.31 – 0.58; 95% CI; p<0.001) compared to unvaccinated. In the second half of the observation period, unvaccinated HCWs had a RR of 0.21 (0.18 – 0.25; 95% CI; p<0.001) as compared to the first one. A linear regression model (R2 = 0.87) showed that every percent increase in vaccinated HCWs lowered daily incidence by 0.94 (0.86 – 1.02; IC 95%; p<0.001). Vaccinated HCWs had a RR of 0.09 (0.07 – 0.12; 95% CI; p<0.001) compared to unvaccinated HCWs, which led to estimated effectiveness of the two-dose vaccine of 91 % (± 3 %; CI 95%) similar to that reported by the manufacturer.*

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and the consequent Coronavirus Disease 2019 (COVID-19) have affected over 170 million people across more than 200 countries at the time of the study (1). Since the World Health Organization (WHO) declared the emergency status for the COVID-19 pandemic on March 11th, 2020, over 3 million people have died (2, 3). In order to counter the spread of the infection, an unprecedented international effort was per-

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formed by private and public institutions to develop a vaccine against its causative agent, SARS-CoV-2, and to quickly administer it to the whole global population (4, 5).

Safe and effective prophylactic vaccines are urgently needed to contain the pandemic, which is having devastating medical, financial and social consequences. Extensive vaccination of people at high risk first, and later of the general population, is the single most effective public health measure for the mitigation of COVID-19 pandemic (6, 7).

The regulatory framework for COVID-19 vaccines is being developed and updated by National Authorities like the European Medicines Agency (EMA) (8) or the Food and Drug Administration (FDA). The first three COVID-19 vaccine products authorized by the European Union (Pfizer/BioNTech BNT162b2 COVID-19 Vaccine, Moderna mRNA-1273 vaccine and AstraZeneca/ChAdOx1-S recombinant vaccine) are recommended to be administered in a two-dose regimen to prime the individual immune response (9, 10), and a third dose is recommended to provide added protection against COVID-19 infection for those vaccinated six months ago (11).

In December 2020 EMA approved the Pfizer-BioNTech COVID-19 vaccine (BNT162b2; Pfizer Inc), based on interim analyses from phase 3 randomized controlled trials (12, 13). The Pfizer–BioNTech COVID-19 vaccine, sold under the brand name" Comirnaty" (14), is a mRNA-based COVID-19 vaccine. It is composed of nucleoside-modified mRNA (modRNA) (15) encoding the SARS-CoV-2 full-length spike protein, modified by two prolines mutations and encapsulated in lipid nanoparticles (BNT162b2) (16, 17). A two-dose regimen of BNT162b2 (30 μg per dose, given 21 days apart) was found to be safe and 95% effective against Covid-19 (18). Randomized clinical trials of mRNA-based vaccines reported efficacies for preventing coronavirus 2019 (Covid-19) in the range of 94% to 95% (19,20).

During October 2020 – January 2021, Italy experienced the second wave of the pandemic, with an unprecedented surge in COVID-19 incidence that led to a new national lockdown. In late December 2020 Italy started its mass COVID-19 immunization campaign, beginning with healthcare workers (HCWs) for their higher risk of workplace exposure and of transmission to vulnerable patients (21, 22). The campaign began on December 27th 2020, with mass vaccination of HCWs from January 2021 (23, 24).

"Città della Salute e della Scienza" of Turin, one of the largest Italian hospitals, started a vaccination campaign of about 13,787 HCWs on December 27th, 2020: 9,843 among eligible staff members received two doses of BNT162b2 from the Infection Prevention and Control Unit of this Hospital in about 4 months. The present study leveraged the integrated data repositories to evaluate COVID-19 vaccine effectiveness. Relying on this observational data set and on those of the Province of Turin, the study assessed the post vaccination situation among HCWs and the association between Pfizer/BioNTech BNT162b2 COVID-19 Vaccine and SARS-CoV-2 infections after the fulfillment of the two-dose vaccination schedule.

Methods

Study design

This observational prospective study was designed with a population of 13,787 HCWs, including non-permanent staff such as medical residents, students, volunteers, specialized technicians, and matched the HCWs cohort after the vaccination campaign with the two doses Pfizer/BioNTech BNT162b2 COVID-19 vaccine to the cases of the Province of Turin. In order to assess vaccine-associated reductions in the rate of infections, the observation started on October 1st, 2020 until April 30th, 2021. The period in study was divided in two splits, the first one starting from October 1st until January 14th, the second one starting from January 15th until April 30th. That timeline was chosen mainly for two reasons: to witness the Italian second wave of the pandemic (started in early October), and to detect differences due to vaccination, as January 15th was in the middle of the vaccinal campaign, with January 18th seeing the first second doses administered. In order to have a comparison with the out-of-hospital scenario, data was gathered about all the new SARS-CoV-2 positive cases during the whole period in the Province of Turin; then the incidence rates of the two different populations were calculated and differenc-

es between the incidences were analyzed. This pattern was possible using observational data collected by the hospital's Infection Prevention and Control Unit, which kept on the scrupulous surveillance of vaccinated and unvaccinated staff during the second period (from January 15th to April 30th). In addition, SARS-CoV-2 tests were carried out in the hospital central laboratory, offering the opportunity to track post-vaccination infections. Using this observational model, two different groups were considered (unvaccinated and vaccinated) among positive cases, to obtain a more accurate estimate of the difference between the province incidence and the hospital incidence. Post-vaccination SARS-CoV-2 infection was always confirmed by a PCR test, according to the screening policy of the hospital. Incidence rates of vaccinated and unvaccinated HCWs were calculated and compared to the general population rates. A descriptive analysis was conducted examining the characteristics of the cohort of positive fully vaccinated cases, diversifying in accordance with sex (female/male), age (years), length of positivity time (time between positive PCR test and first negative PCR test), distance from 2nd dose, sites of contagion, symptomatic/asymptomatic, healthcare working sector (medical, surgical or administrative area).

Inclusion criteria

The main inclusion criterion for HCWs was the employment by "Città della Salute e della Scienza" between October 1st, 2020 and April 30th, 2020. Included HCWs belonged to different healthcare sectors and worked on various wards with different probabilities of exposure. Non-permanent staff such as medical residents, specialized students, volunteers and specialized technicians was included as well. The inclusion criterion for the province of Turin was the obtainment of a positive swab; the regional database provides the numbers of the daily new positive cases subdivided for provinces.

Outcomes

The study aimed to describe early vaccine effectiveness of the Pfizer/BioNTech BNT162b2 COVID-19 Vaccine in accordance with a decrease of infections in the HCWs large-scale cohort of "Città della Salute e della Scienza". The primary outcome was the impact of vaccination on the intra-hospital epidemic, normalized for the trend of SARS-CoV-2 infections in the province of Turin, described by differences in infection rates between the HCWs population and the general population and between the vaccinated and unvaccinated HCWs population.

Data gathering

All positive PCR tests for SARS-CoV-2 among HCWs restricted to the period from October 1st 2020 to January 14th 2021 and from January 15th to April 30th 2021 were gathered. All HCWs with at least one positive SARS-CoV-2 PCR test (anterior nasal swabs or combined nose and oropharyngeal swabs) made by or presented to the Infection Prevention and Control Unit were defined as cases of SARS-CoV-2 infection. Positive HCWs could have been tested by the Infection Prevention and Control Unit for one of the following criteria: 1) presenting COVID-19 compatible symptoms, 2) close contact with any known positive case, 3) routine test for workers in high-risk zones, 4) any positive Antigen test, which had to be confirmed by a RT-PCR test (25). The study database used data linkage with the laboratory surveillance system to extract positive test results during the observed period (October to April). In order to retrieve COVID-19 data of the Province of Turin, access was gained to the Piedmont Region COVID-19 database: it was updated daily with the number of new PCR-test positive cases. Regarding the in-hospital mass vaccination campaign, data was gathered about daily numbers of vaccines, divided by first and second doses. The new positive cases were divided from January 18th in vaccinated and unvaccinated; January 18th was chosen because it was the first day in which second doses were injected (the vaccination campaign started 21 days before, on December 27th, 2020). A descriptive analysis was conducted about the vaccinated HCWs cohort, including general characteristics and information about the infection (with or without symptoms, time elapsed from the first positive test to the first negative test).

Statistical analysis

Cumulative incidence curves for the vaccinated and unvaccinated groups were calculated and tested with t-Student test as mean incidence rates. This comparison allowed to calculate the gap in the rate of new cases. Then, the overall risk ratios (RR) were calculated using $\chi 2$ test for the vaccinated group compared to the general population and the unvaccinated group, and for the unvaccinated group in the first and second period compared to the general population and to itself in the two periods. To correctly evaluate the RR, as reference were used the total days of observation for unvaccinated and vaccinated HCWs, to avoid a methodological bias due to the progressive variation in number of the two subgroups; the observation time started on January 25th, 1 week after the first second doses. The same reference was used to estimate RR between vaccinated HCWs and the general population. To better study and understand the difference in probability of infection, a Kaplan-Meier risk function was calculated for the vaccinated and unvaccinated HCWs subgroups. Vaccine effectiveness was evaluated as one minus the risk ratio ((1 – HR) × 100) . A linear regression was modelled to correlate the intra-hospital incidence (as dependent variable) to the out-of-hospital incidence and the percentage of vaccinated HCWs.

Results

Outcomes were restricted to the period from October 1st, 2020 to April 30th, 2021: throughout the period analyzed, 13,787 HCWs met inclusion criteria and were included in this prospective observational study.

Variables regarding the dynamics of the pandemic inside and outside the Hospital in the whole timeframe and divided per the two periods in study are reported in Table 1; incidence rates and their mobile averages, from the start of the pandemic and restricted to the periods in study, are depicted in Figures 1, 2 and 3.

The cohort of positive cases had an average age of 46.43 years (± 0.60; 95% CI) with a median of 48 years; it was composed of 362 men (26.40 %) and 1,009 women (73.60 %). The vast majority (1331; 97.08 %) of the positive tests were performed by the hospital Infection Prevention and Control Unit; 40 (2.92 %) positive tests were instead performed outside the hospital. One COVID-19 related death occurred among the HCWs cohort throughout the period in study.

In the first period, HCWs incidence was higher than the incidence of the province with a statistically significant difference (+41.04 ±13.47 daily new cases/100,000; CI 95%; $p<0.001$). In the second period, however, the situation was reversed: incidence

Table 1. Pandemic variables regarding the two periods in study: October 1st to January 14th, January 15th to April 30th

Populations		HCWs	Province of Turin
Overall			
	New Cases, N.	1,371	167,400
	Daily Average, N.	6.47 (± 1.25; 95% CI)	790 (± 75; 95% CI)
	Incidence, N./100,000	47.5 (± 9; 95% CI)	35.05 (± 3.35; 95% CI)
	Prevalence, %	9.94 %	7.41 %
1st Period			
	New Cases, N.	1,163	92,262
	Daily Average, N.	10.97 (± 2.15; 95% CI)	940 (± 149; 95% CI)
	Incidence, N./100,000	79.58 (± 15.58; 95% CI)	38.54 (± 5.96; 95% CI)
	Prevalence, %	8.44 %	4.08 %
2nd Period			
	New Cases, N.	208	75,138
	Daily Average, N.	1.96 (± 0.38; 95% CI)	770 (± 72; 95% CI)
	Incidence, N./100,000	14.23 (± 2.73; 95% CI)	31.56 (± 2.95; 95% CI)
	Prevalence, %	1.51 %	3.32 %

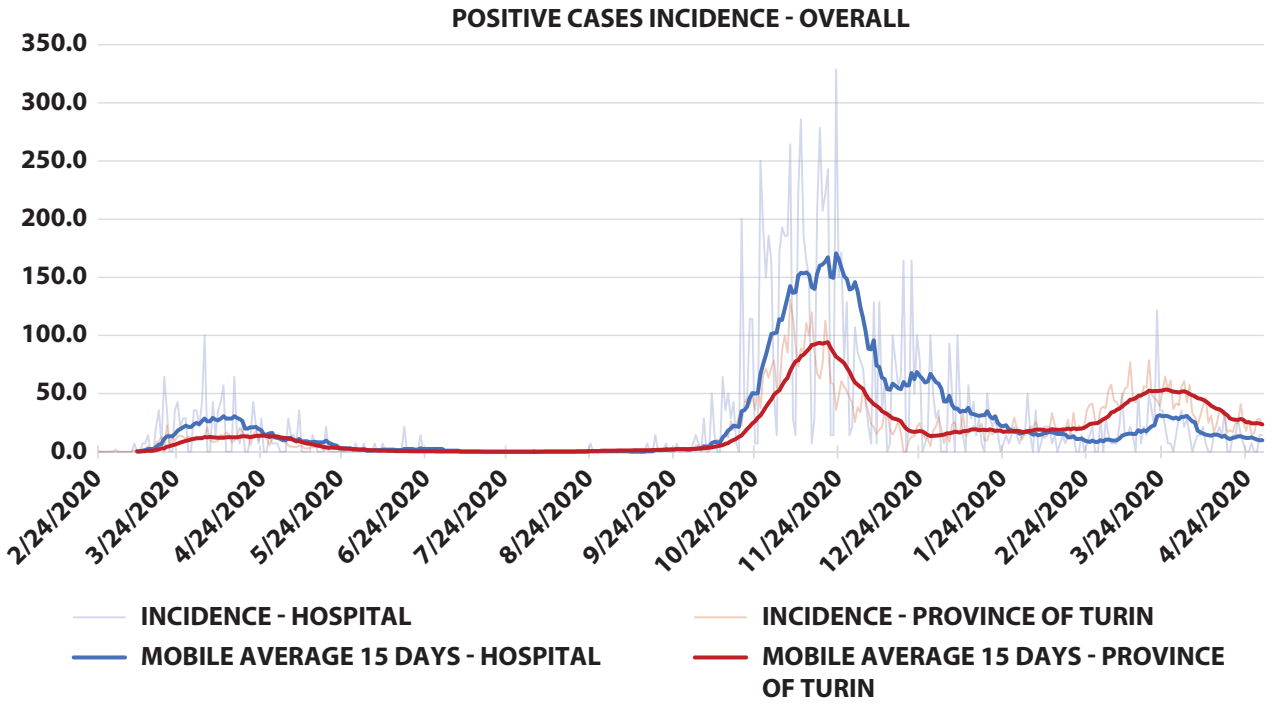

Figure 1. Positive cases incidence from the beginning of the pandemic. Data is represented as daily incidence rates.

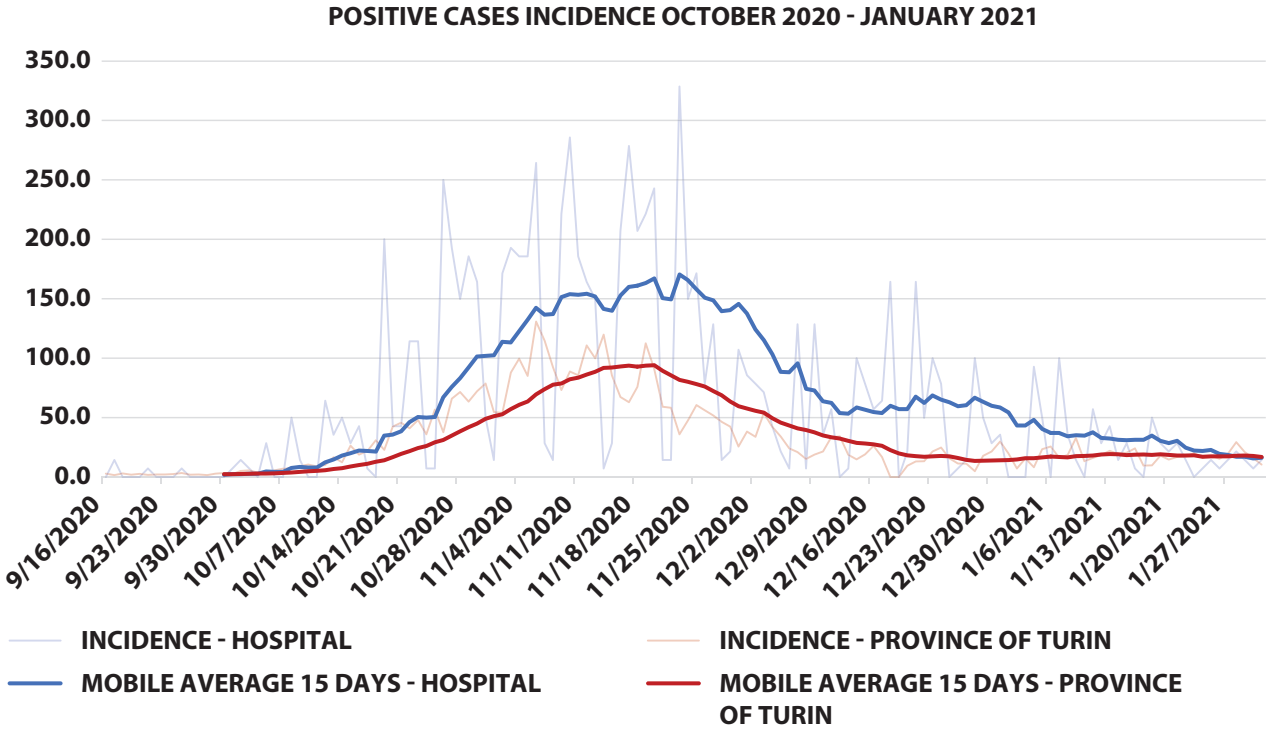

Figure 2. Positive cases incidence during the first period in study. Data is represented as daily incidence rates

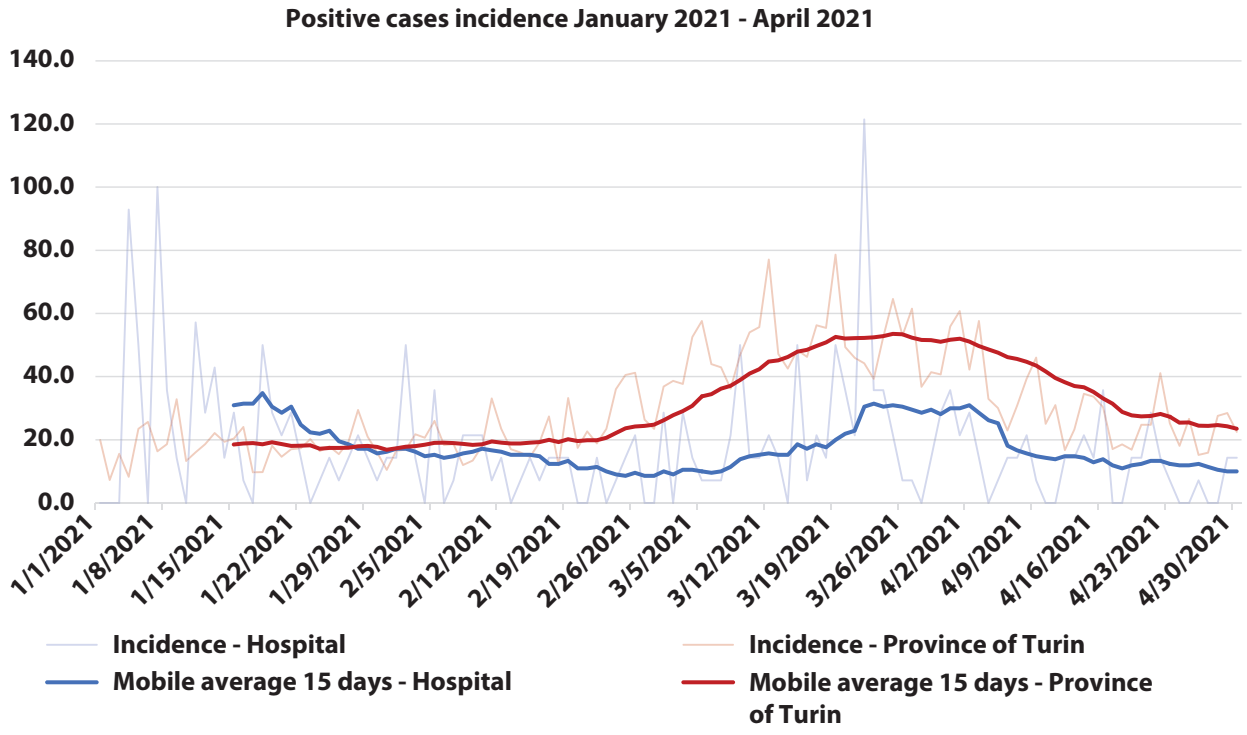

Figure 3. Positive cases incidence during the second period in study. Data is represented as daily incidence rates

rate among HCWs was lower than the province's one, marking a statistically significant difference (-17.32 ± 3.57; CI 95 %; p <0.001).

Of the total, 9,843 (71.39 %) HCWs received full vaccination from the start of the vaccinal campaign to April 30th, with a mean of 193 daily administered doses. Almost all the fully vaccinated HCWs received the second dose 21 or 22 days after the first dose. About 3,944 (28.61 %) HCWs remained unvaccinated at the date of the study; a part of the latter completed the full vaccination cycle in the following period. During the second period, 59 (28.3 %) vaccinated HCWs and 149 (71.7 %) unvaccinated HCWs had a new positive test for SARS-CoV-2.

The two groups were divided considering HCWs as "vaccinated" 1 week after the second dose of the vaccine was given. Thus, incidence rates were calculated among two varying populations (the subgroup of vaccinated HCWs increased along the period, at the expense of the unvaccinated HCWs subgroup). The mean daily incidence rate for vaccinated HCWs was 6.30 (± 2.66; 95% CI) new cases/100,000, while for unvaccinated HCWs the average daily incidence was 22.82 (±4.67; 95% CI) new cases/100,00; vaccinated HCWs had a reduced risk of infection compared to unvaccinated HCWs (-16.52 ± 5.01; 95% CI; p<0.001) and to the general population (-25.26 ± 3.40; 95% CI; p<0.001). The relative risk of infection during the studied period was 0.17 (0.13 – 0.22; 95% CI; p<0001) for the vaccinated group compared to the general population, 0.43 (0.31 – 0.58; 95% CI; p<0.0001) compared to the unvaccinated HCWs group (during the second period) and 0.09 (0.07 – 0.12; 95% CI; p<0.0001) compared to unvaccinated HCWs during the first period. The unvaccinated group had a lower risk of infection compared to the general population of 0.50 (0.42 – 0.58; 95% CI; p=0.0001), considerably lower in comparison to the first period, when all HCWs were unvaccinated and had a RR compared to the general population of 2.07 (1.96 – 2.18; 95% CI; p<0.0001). Unvaccinated HCWs had a lowered relative risk of infection between the first and the second period of 0.21 (0.18 – 0.25; 95% CI; p>0.0001).

A linear regression model was built using daily SARS-CoV-2 incidence rate as the dependent vari-

able and the percentage of fully vaccinated HCWs along with the daily incidence rate of the province of Turin as independent variables. The model had a 0.87 R2 and allowed to observe as each unit increase in the % of the number of fully vaccinated HCWs (unitary increase equivalent to about 137 people), there was a decrease of 0.936 (0.857 – 1.015; 95% CI; p <0.001) in the daily incidence of infections among HCWs (table 2). Nonetheless, at each unitary increase in the province incidence, there was an increase of 1.555 (1.452 – 1.659; 95% CI; p <0.001) in the hospital incidence.

The spread of infection was analyzed from January 2021 to April 2021, divided in vaccinated and unvaccinated groups, represented in figure 4.

To better understand the evolution of the two different populations a risk function of infection was calculated between the unvaccinated and vaccinated participants using the Kaplan-Meier risk function estimator. HCWs presented a different risk of infection depending on vaccinal status: vaccinated hospital staff showed a constant reduction in the risk of infection during the three months in analysis (p <0.001 according to Mantel-Cox). As highlighted before, during the second period the relative risk of infection was approximately doubled for unvaccinated personnel (RR = 2.35 (1.74 – 3.17; 95%CI; p<0.0001). Variables regarding this calculation has been visually represented in figure 5.

The adjusted risk ratio was used to calculate the effectiveness of the vaccine: it was inferred as one minus the risk ratio for vaccinated HCWs (1-0.436) x100, showing an efficacy of the vaccine of 57.44 % (± 4 %; CI 95 %). Compared to the general population,

Table 2. Linear regression model with R^2 0.87

Variables	Beta Coefficient	Standard Error	95% CI	p-value
Positive cases incidence (Province of Turin)	+1.555	0.040	1.452 | 1.659	<0.001
% of fully vaccinated HCWs	-0.936	0.052	-1.015 | -0.857	<0.001

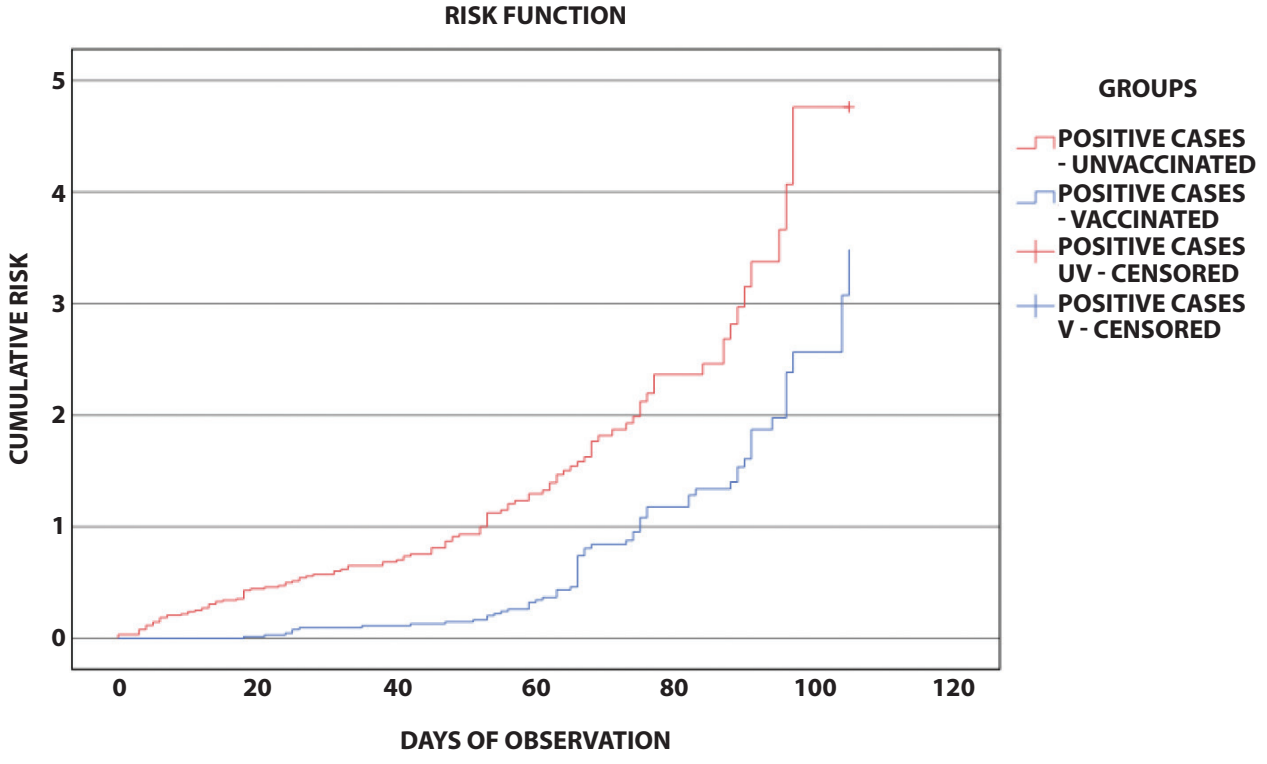

Figure 4. Kaplan-Meier risk function for new positive cases in the Vaccinated and Unvaccinated groups

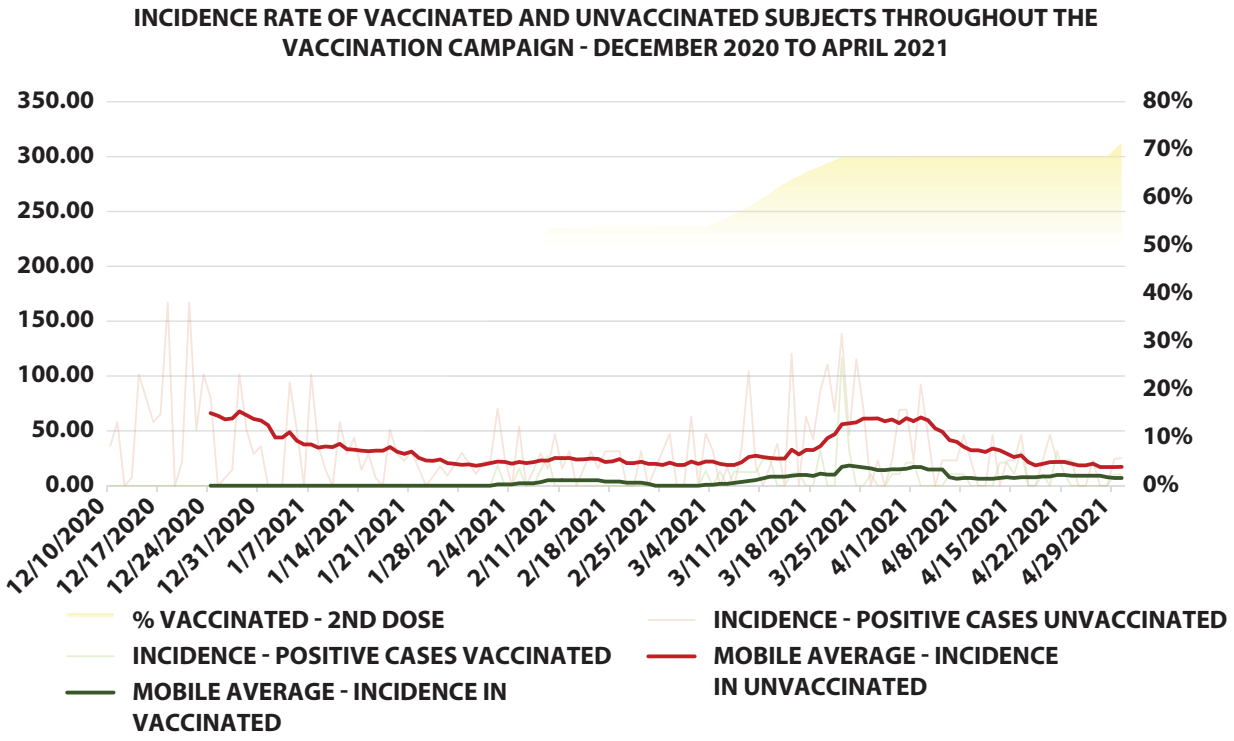

Figure 5. Daily incidence of positive cases in the Vaccinated and Unvaccinated groups compared to the % of fully vaccinated HCWs

the vaccine efficacy soared at 83 % (± 5 %; CI 95 %). Compared to HCWs in the first period, the vaccine efficacy was even higher at 91 % (± 3 %; CI 95%).

Among the 59 positives post-vaccination traced with PCR test the average age was 49 years: 12 members were under 40 years (20.34%), 40 were aged 40-60 years (67.80%) and 7 were over 60 years (11.86%). The group was composed of 40 women (67.8%) and 19 men (32.2%). Only 2 HCWs tested positive 7 to 14 days after the second vaccination (3.39%), 56 tested positive 15 or more days after the second vaccination (94.94%) and 1 person had a PCR test positive <7days from the second dose of Pfizer–BioNTech COVID-19 vaccine. The mean time and median from vaccination were both estimated both at 56 days . The length of positivity time (time between positive PCR test and first negative PCR test) was an average time of 13 days with a median 11 days. They belonged to different healthcare sectors and worked on various wards: 26 worked in the surgical area (44%), 29 in the medical area (49 %), 4 in administrative area (7%). Descriptive variables of this small cohort are reported in Table 3.

Results show that there were 42 asymptomatic HCWs (71%) and 17 symptomatic HCWs (29%). Among HCWs who had the onset of clinical manifestations there was evidence of mild symptoms (headache, fever, cough, myalgia and sore throat) without any severe pneumonia or hospitalization. Asymptomatic cases were identified among HCWs as part of post-exposure surveillance with PCR test.

The Prevention and Control Unit registered 9 HCWs (15.28%) that supposedly had community-related exposures, 14 (23.72%) that contracted the infection from patients, 18 (30.5%) from households and 18 (30.5%) from hospital staff members. However, any of the SARS-CoV-2 clusters was linked to vaccinated HCWs.

Discussion

Since "Città della salute e della Scienza" began HCWs vaccination on December 27th, 2020, this observational study evaluated the effectiveness of

Table 3. Descriptive analysis of the positive vaccinated cases cohort (N.= 59)

	N.	%
Age (years)		
<40	12	20.34 %
40-59	40	67.80 %
>60	7	11.86 %
Sex		
Female	40	67.80 %
Male	19	32.20 %
Employment sector		
Administrative	4	7 %
Medical area	29	49 %
Surgical area	26	44 %
Distance from 2nd dose		
<7 days	1	1.69 %
7 to 14 days	2	3.39 %
≥ 15 days	56	94.92 %
Clinical features		
Asymptomatic	42	71 %
Symptomatic	17	29 %
Reported exposure		
Community-related	9	15.28 %
Workplace-related	14	23.72 %
Households-related	18	30.5 %
Staff-related	18	30.5 %

the Pfizer/BioNTech BNT162b2 COVID-19 vaccine in an extensive vaccination campaign. Collected data showed an early vaccine efficacy in preventing SARS-CoV-2 infection of 91% after 7 days from the second dose administration. Considering the incidence rates between hospital and province of Turin, an early reduction in SARS-CoV-2 infection among HCWs could be observed, especially in the vaccinated group. The strongest association between the introduction of vaccination and the decrease in documented SARS-CoV-2 infections can be visually observed in Figure 1 from February 1st onwards, when the two incidence curves intersect and switch positions; the timing allows to assume that it is the effect of the vaccination campaign. Furthermore, a slight decrease of the new cases incidence can be seen at the end of the first period both for HCWs and the province of Turin: this can be explained by the effectiveness of the prophylactic measures undertaken in the prior months by the Italian Government.

From October 1st, 2020 to January 14th, 2021 incidence rate of SARS-CoV-2 infection was lower in the province of Turin compared to the incidence rate among HCWs in a statistically different way, as seen in Figure 2. This marked difference in the spread of the virus could be explained by the HCWs' higher risk of infection, mainly due to their professional exposure (26). In addition, this outcome is a result of close monitoring carried out by the hospital's Infection Prevention and Control Unit, based on a strict protocol that allowed to trace most of the asymptomatic HCWs, opposed to the general population, where many cases have not been detected due to the scarcity of diagnostic power in comparison to the target population. Two abnormal peaks can be seen in the hospital's incidence rate curve (during the second half of December 2020 and the second half of March 2021), most likely resulting from the growing number of hospitalizations following the considerable rise of cases in the province of Turin during the previous two weeks.

Considering the two subgroups of vaccinated and unvaccinated HCWs in the second period, a reduction in the RR of infection for vaccinated HCWs could be observed in comparison of unvaccinated HCWs and the general population, but the highest reduction in the RR of infection occurred between HCWs in the first period and vaccinated HCWs in the second period. Interestingly, the RR of infection of unvaccinated HCWs in comparison to the general population inverted between the first and the second period: unvaccinated HCWs were still less at risk compared to the general population. This result could partly be explained with a general reduction of incidence in the province, providing for better and more accurate care, but it is reasonable to say that, given the high risk of contagion between HCWs, vaccinated HCWs generated an in-hospital herd protection effect.

Amongst the total of HCWs, 3,944 still remained unvaccinated on April 30th. This group of unvaccinated staff members was composed by a mix of HCWs who refused to join the vaccination campaign, HCWs who could not be vaccinated because of SARS-CoV-2 infection contracted over the previous three months, HCWs for whom the

vaccination was contraindicated and HCWs who had to undergo specialistic evaluation prior to the vaccination for underlying health conditions (mostly for allergologic issues). The sharp difference between the two groups has been visible since the introduction of the vaccine variable, increasing progressively from the first days of February until the end of April. As an evidence of what was reported, the linear regression model showed a marked impact of the two variables in study (the out-of-hospital incidence rate and the percentage of vaccinated HCWs) on the in-hospital incidence, with an high reliability underlined by an R^2 of 0.87; the unitary percentage increase in the number of people vaccinated (corresponding to roughly 137 HCWs), corrected for the general population incidence, led to a decrease of 0.936 in the daily incidence of infections among the HCWs population. Assuming this result, approximately every 7% of vaccinated HCWs the daily incidence reduction carried one daily case less; considering that the hospital vaccinated 1.5 % of HCWs daily, every five days there was on average a reduction of one daily case.

The vaccine efficacy calculation was carried out using three different RR, but the comparison most adherent to reality is likewise the one between vaccinated HCWs and unvaccinated HCWs in the first period in study. The comparison between vaccinated and unvaccinated HCWs during the second period is inevitably biased by the visible herd protection effect, and the comparison with the general population does not consider the higher risk of infection for HCWs. Using the chosen comparison, the adjusted RR for the vaccinated group was 0.09, corresponding to an estimated vaccine effectiveness of 91 %. This result is comparable to the 95% efficacy reported in the phase 3 randomized clinical trials (18) and to recent observational studies in Israel (20, 30, 34), UK (21, 31), US (32) and Italy (33).

Only 1 HCW tested positive within 3 days after dose two, but most likely he was already positive to SARS-CoV-2 during administration (table 3). Full immunization was defined as more than 7 days after receipt of the second vaccine dose. The length of positivity time (time between the first positive PCR test and the first negative PCR test) was on average 13 days, with a median of 11: this result has been influenced by the fact that one of the three departments of "Città della Salute e della Scienza" performed the control test and the serological examination from 3 to 5 days after the first positivity, instead of after 10 days like the two others. The Prevention and Control Unit registered a lowering in intrahospital exposures, with any SARS-CoV-2 cluster linked to the HCWs: this aspect can explain the effectiveness of vaccination, as it shows that the intrahospital risk of contagion collapsed, as also underlined by current literature (33). Of note, HCWs who tested positive for SARS-CoV-2 after receiving the first vaccine dose were not eligible to receive the second dose, according to the EMA policies (9), and so they were not considered in the study.

This study has some limitations, linked on the one hand to its observational nature, on the other hand to the difficult tasks of gathering, reordering and matching variables regarding large cohorts. Firstly, differences in demographic characteristics and socioeconomic status between residents of the province of Turin and the HCWs in the hospital have not been considered. The hospital cannot be representative of the general population: HCWs were younger and had an overall higher risk of exposure to SARS-CoV-2 than normal population. Furthermore, in the comparison of the incidence rates of the two curves (hospital and province of Turin), the number of swabs is different between the general population and HCWs; in fact, the latter underwent a closer surveillance by the hospital's Infection Prevention and Control Unit as exposed to a continuous risk of infection for the entire period analyzed. In the second period, between January 15th, 2021and April 30th, 2021, vaccinated HCWs underwent fewer PCR tests for SARS-CoV-2 infection than unvaccinated, potentially underestimating the number of asymptomatic cases in the vaccinated group who were not regularly screened. Lastly, the out of hospital vaccination campaign was not taken into account due to the very low percentage of fully vaccinated patients at the time of the study, that capped at around 10% of the population at the end of April (of which a considerable proportion was composed of vaccinated HCWs); considering the vaccinated percentage of the general population could have strengthened the results regarding vaccine

effectiveness, but the risk of biased data was too high. From a methodological point of view, Student's test could have a level of uncertainty in unskewed samples like the ones taken into account in the first part of the study (the HCWs cohort and the population of the province of Turin). Vaccine effectiveness has been evaluated only from a diagnostic point of view; COVID-19 related deaths among the populations in study were not considered, and symptoms were evaluated just in a descriptive way only in the positive vaccinated HCWs subgroup.

Conclusions

This study highlighted the significant impact of mass vaccination on the trend of SARS-CoV-2 infections among HCWs and hospital facilities. A high efficacy of the Pfizer/BioNTech Bnt162b2 COVID Vaccine was found not only in protecting vaccinated HCWs, but also in generating a herd protection effect potentially capable of keeping out of risk even unvaccinated HCWs. The implementation of this prevention measure is strongly needed to mitigate the pandemic spread of COVID-19. This result could contribute to the promotion of the vaccination campaign in the general population and in health professionals not yet vaccinated. More studies are needed to evaluate new cases of infections in fully vaccinated HCWs.

Declaration of Interest: The authors declare no conflict of interest.

References

1. World Health Organization. Coronavirus Disease (COVID-19) Situation Dashboard.; 2021. Accessed June 10, 2021. https://covid19.who.int/
2. World Health Organization. WHO Director-General's Opening Remarks at the Media Briefing on COVID-19 — 11 March 2020.; 2020. Accessed June 10, 2021. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19
3. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. 2021.; 2021. Accessed June 10, 2021. https://covid19.who.int/
4. Krammer F. SARS-CoV-2 vaccines in development. *Nature*. 2020;586(7830):516-527. doi:10.1038/s41586-020-2798-3
5. Rego GNA, Nucci MP, Alves AH, et al. Current clinical trials protocols and the global effort for immunization against sars-cov-2. *Vaccines*. 2020;8(3):1-44. doi:10.3390/vaccines8030474
6. Hasan T, Beardsley J, Marais BJ, Nguyen TA, Fox GJ. The implementation of mass-vaccination against SARS-CoV-2: A systematic review of existing strategies and guidelines. *Vaccines*. 2021;9(4). doi:10.3390/vaccines9040326
7. WHO. World Health Organisation. WHO Issues Its First Emergency Use Validation for a COVID-19 Vaccine and Emphasizes Need for Equitable Global Access (Media Release).; 2020. Accessed June 10, 2021. http://www.who.int.
8. EMA. European Medicines Agency (EMA). Preparing guidance to tackle COVID-19 variants. EMA News. 10 February 2021. Published online February 10, 2021. Accessed June 10, 2021. https://www.ema.europa.eu/en/news/ema-preparing-guidance-tackle-covid-19-variants
9. EMA. European Medicines Agency (EMA). COVID-19 vaccines. Overview 2021. Published online 2021. Accessed June 10, 2021. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines (Accessed November 6, 2021)
10. ECDC. Risk of SARS-CoV-2 Transmission from Newly-Infected Individuals with Documented Previous Infection or Vaccination.; 2021. https://www.ecdc.europa.eu/en/publications-data/sars-cov-2-transmission-newly-infected-individuals-previous-infection (Accessed November 6, 2021)
11. Saciuk Y, Kertes J, Shamir Stein N, Ekka Zohar A. Effectiveness of a third dose of BNT162b2 mRNA vaccine [published online ahead of print, 2021 Nov 2]. *J Infect Dis*. 2021;jiab556. doi:10.1093/infdis/jiab556
12. Lamb YN. BNT162b2 mRNA COVID-19 Vaccine: First Approval. *Drugs*. 2021;81(4):495-501. doi:10.1007/s40265-021-01480-7
13. PFIZER. Pfizer and BioNTech Achieve First Authorization in the World for a Vaccine to Combat COVID-19 (Media Release). 2 Dec 2020. Lancet. 2021; 2021. Accessed June 10, 2021. http://www.pfizer.com.
14. EMA. "Comirnaty EPAR". European Medicines Agency (EMA). https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty (Accessed November 6, 2021)
15. Karikó K, Muramatsu H, Welsh FA, et al. Incorporation of pseudouridine into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability. *Molecular Therapy*. 2008;16(11). doi:10.1038/mt.2008.200
16. Walsh EE, Frenck RW, Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *N Engl J Med*. 2020;383(25). doi:10.1056/nejmoa2027906

17. Pardi N, Tuyishime S, Muramatsu H, et al. Expression kinetics of nucleoside-modified mRNA delivered in lipid nanoparticles to mice by various routes. *J Control Release*. 2015;217:345-351. doi:10.1016/j.jconrel.2015.08.007
18. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603-2615. doi:10.1056/nejmoa2034577
19. Baden LR, el Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403-416. doi:10.1056/nejmoa2035389
20. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med*. 2021;384(15):1412-1423. doi:10.1056/nejmoa2101765
21. Hall VJ, Foulkes S, Saei A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. *Lancet*. 2021; 397 (10286): 1725-1735. doi:10.1016/S0140-6736(21)00790-X
22. Hassan-Smith Z, Hanif W, Khunti K. Who should be prioritised for COVID-19 vaccines? *Lancet*. 2020;396(10264). doi:10.1016/S0140-6736(20)32224-8
23. ISS. Vaccine Day Il 27 Dicembre in Tutta Italia e in Europa ISS (Ministero Della Salute).; 2020. Accessed June 10, 2021. https://www.salute.gov.it/portale/news/
24. Comunicato AIFA n. 620 - Autorizzato il vaccino BioNTech Pfizer. AIFA. Published online December 22, 2020.
25. Coggiola M, Cavallo R, Grillo E, et al. SARS-CoV-2 infection: Use and efficacy of antigen swab for the health surveillance of healthcare workers. *Med Lav* 2021; 112 (6): xxx-xxx
26. Ran L, Chen X, Wang Y, Wu W, Zhang L, Tan X. Risk Factors of Healthcare Workers With Coronavirus Disease 2019: A Retrospective Cohort Study in a Designated Hospital of Wuhan in China. *Clin Infect Dis*. 2020;71(16):2218-2221. doi:10.1093/cid/ciaa287
27. Shah ASV, Wood R, Gribben C, et al. Risk of hospital admission with coronavirus disease 2019 in healthcare workers and their households: Nationwide linkage cohort study. *The BMJ*. 2020;371. doi:10.1136/bmj.m3582
28. Istituto Superiore di Sanità. Impatto della vaccinazione COVID-19 sul rischio di infezione da SARS-CoV-2 e successivo ricovero e decesso in Italia (27.12.2020 - 03.05.2021). https://www.epicentro.iss.it/vaccini/pdf/report-valutazione-impatto-vaccinazione-covid-19-15-mag-2021.pdf
29. Keehner J, Horton LE, Pfeffer MA, et al. SARS-CoV-2 Infection after Vaccination in Health Care Workers in California. *N Engl J Med*. 2021;384(18):1774-1775. doi:10.1056/NEJMc2101927
30. More on SARS-CoV-2 Infection after Vaccination in Health Care Workers. *N Engl J Med*. Published online 2021. doi:10.1056/nejmc2106004
31. Angel Y, Spitzer A, Henig O, et al. Association between Vaccination with BNT162b2 and Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infections among Health Care Workers. JAMA. Published online 2021. doi:10.1001/jama.2021.7152
32. Thompson MG, Burgess JL, Naleway AL, et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(13):495-500. Published 2021 Apr 2. doi:10.15585/mmwr.mm7013e3
33. Fabiani M, Ramigni M, Gobbetto V, Mateo-Urdiales A, Pezzotti P, Piovesan C. Effectiveness of the comirnaty (BNT162b2, BioNTech/Pfizer) vaccine in preventing SARS-CoV-2 infection among healthcare workers, Treviso province, Veneto region, Italy, 27 December 2020 to 24 March 2021. *Eurosurveillance*. 2021;26(17):1-7. doi:10.2807/1560-7917.ES.2021.26.17.2100420
34. Amit S, Beni SA, Biber A, Grinberg A, Leshem E, Regev-Yochay G. Postvaccination COVID-19 among Healthcare Workers, Israel. *Emerg Infect Dis*. 2021;27(4):1220-1222. doi:10.3201/eid2704.210016