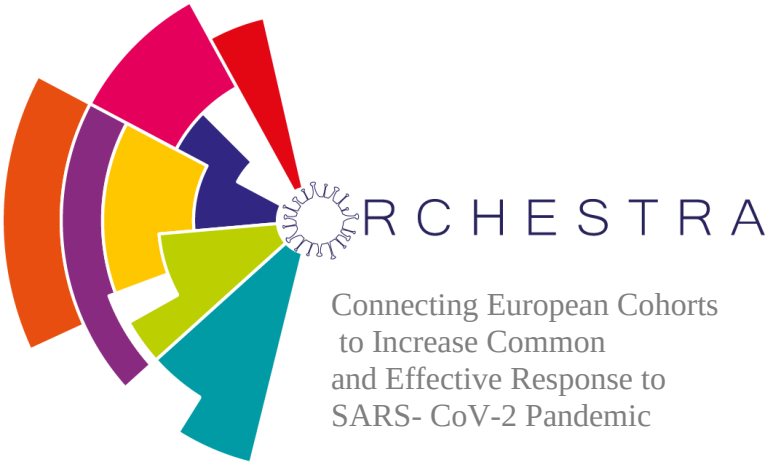

DELIVERABLE

WP5_D5.6
Immunological response in vaccinated and not vaccinated HCWs (temporal trend) final

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Executive Summary

We calculated the distribution and determinants of the difference between two serological measurement of anti-COVID-19 S1 antibodies in 19,422 healthcare workers (HCW) from Italy (Bari, Bologna, Brescia, Trieste and Verona), Spain (Barcelona and Oviedo), Romania (multicentric cohort) and Slovakia (multicentric cohort), who received two or three vaccine doses and were tested within a 13-month period following the first vaccine dose. Since different test methods were used across the cohorts, differences in serological level were divided by the standard error (SE) of the cohort-specific distribution. We conducted descriptive analyses and fitted multivariate linear regression models to identify factors associated with the difference between the two serological measurements.

We observed a progressively reduced difference between the two measurements from <30 days to 210-240 days (ranging among 0.74 and -0.30 SE). No substantial difference was found by time between first serology and first vaccination (-0.30 and -0.32 SE). A total of 94% of HCW received two doses of vaccine; among them, the difference in antibody level between the two doses was negative; while among HCW who received three vaccine doses the difference was positive because the second measurement was made close to the third dose. Women were slightly more likely to register a greater difference in serological measurements than men, while age was associated with a decrease. No difference was found by job title. When considering previous COVID-19 infection, the HCW who got infected between the two serological measurements had a greater difference compared to the never infected. Those infected before the first serological measurement resulted to have 1.22-fold higher difference between serologies (95% confidence interval [CI]=1.17-1.28). Time between first vaccine dose and first serology was associated with a smaller difference in the serological samples (relative risk [RR] 0.91, 95% CI=0.90-0.92 for 30-day increase), as did time in between the two samples (RR 0.95, 95% CI 0.94-0.96 for 30-day increase). Compared to Comirnaty, use of Spikevax resulted to be associated with a greater difference in the two serologies (RR 1.20, 95% CI=1.08-1.34).

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Abbreviations

AIFA, Italian Medicine Agency

CI, confidence interval

HCW, Healthcare worker

INMI, Italian National Institute of Infectious Diseases

RR, relative risk

SE, standard error

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Introduction

Vaccines are of outmost importance for human health, representing one of the first medical intervention which everyone receive at birth as far as they are available in hospital setting.

While childhood vaccinations are usually long-lasting, vaccination in adults is not as durable.

Immune memory depends on the type of vaccine, and a vaccine-specific immunity can vary in different subjects based on individual and environmental factors (1). Live attenuated vaccines are highly able to induce lifelong protection; glycol-conjugated vaccines' immunity duration derives from the characteristics of their carrier. Remarkably, non-adjuvanted vaccines are sufficient for seasonal influenza because population is already primed by previous infection and vaccination; conversely, new virus strains for which people are naïve require adjuvated vaccines, and remain possible cause of new pandemics (1). As reviewed by Castellino and coworkers, H5N1 influenza strain, which spread in 1997 after first occurrence in Hong Kong, was effectively contained by MF59 adjuvated vaccines, which was assessed to be able to induce a high protection 6 months after the administration of one single boost (2). m-RNA vaccines have been largely studied in the last decades and have been assessed to be a valid weapon in case of extreme need, given the very fast manufacturing process (3). Indeed, m-RNA technology – Comirnaty and Spikevax - became the protagonist of COVID-19 pandemic, being decisive in controlling the infection worldwide. Viral-vector vaccines – Vaxzevria - also emerged in the COVID-19 panorama, and were known to represent a possible novel approach in case of pandemic (4).

The introduction of vaccines against COVID-19 helped in limiting the infection spreading, and most importantly determined a substantial reduction of the symptomatic disease and the number of hospitalizations (5, 6). However, the administration of additional boosters with the aim of prolonging their protective effect resulted necessary. This may be due to suboptimal duration of immunization conferred by available vaccines, and the appearance of new COVID-19 variants like Delta and Omicron (7).

ORCHESTRA, a multicenter prospective cohort of health care workers (HCW) from different South-Eastern European countries, was assessed with the aim of investigating COVID-19 infection in the hospital personnel. The objective of the present analysis was to delineate the trends of serological levels in the first 13 months post-vaccination, overall and by month, in a population of about 20 000 HCW based on 9 European study populations (5 from Italy, 2 from Spain, 1 multicentric from Romania and 1 multicentric from Slovakia) included in ORCHESTRA.

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Methods

Data Collection

ORCHESTRA is a prospective multicenter cohort of HCW from several European countries (https://orchestra-cohort.eu). This analysis includes HCW included in nine cohorts from four countries. Data on sociodemographic characteristics, PCR testing, and vaccination status, including date of vaccination doses and type, were either abstracted from medical surveillance records or collected through questionnaires. The levels of anti-COVID-19 S1 antibodies were derived from medical records or generated through ad-hoc testing. Since the cohorts are included in the European Commission-sponsored Orchestra project, their data have undergone extensive harmonization. Details on the methods used for the measurement of antibodies in each cohort were provided in **Deliverable 5.10**.

This study comprises 19,923 HCW from Italy (Bari, Bologna, Brescia, Trieste and Verona), Spain (Barcelona and Oviedo), Romania (multicentric) and Slovakia (multicentric) with multiple serologies during a 13-month timeframe from first dose administration (between December 2020 and March 2021, depending on the cohort), defined as the interval 150-210 days, including the 13-months serology results. After excluding 501 HCW with less than two vaccine doses, 19,422 subjects were included in the analysis.

Data analysis

The outcomes of this analysis were (i) serologic trend of antibodies 1-to-13 months from first dose; (ii) serologic trend of antibodies month-by-month, until 13 months from first dose. Secondary aims were to compare these trends by HCW and vaccines characteristics, including age, sex, study center, previous COVID-19 infection, number of doses, and type of vaccine. Methods of measurement of antibody level varied between the included centers and in the time periods.

We first conducted descriptive analysis of the outcome and explanatory variables. The main analysis consisted in calculating the trend in serological response within 13 months. Multiple linear regression models were used to calculate the relative risks (RR) and their 95% confidence intervals (CI) for the absolute difference between the last and the first serologic measurement, divided by the cohort-specific standard error (standardized value). The models included terms for cohort, sex, age (10-year increase), job title, number of vaccine

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doses received, previous COVID-19 infection, time difference between first serology measure and first dose of vaccine (30 days increase), and time difference between first serology measure and second serology measure (30 days increase). We excluded the HCW who were unvaccinated and those with less than two serological measurements within the 13-month period.

Stata® software 16 (StataCorp LP, College Station, Texas, USA) was used in the statistical analysis. The study was approved by the Italian Medicine Agency (AIFA) and the Ethics Committee of Italian National Institute of Infectious Diseases (INMI) Lazzaro Spallanzani.

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Results

The final analysis included 19,422 HCW with repeated measurements within 13 months after first dose and two or more vaccine doses. Selected characteristics of the study population are described in **Table 1**.

***Table 1**. Distribution of HCWs by selected characteristics and mean difference between second and first standardized serologic measurement*

Variable	N (%)	Mean difference (SE)
Cohort		
Italy-Bari	158 (0.8)	1.20 (0.07)
Italy-Bologna	5 547 (28.3)	-0.28 (0.01)
Italy-Brescia	5 881 (30.0)	-0.33 (0.01)
Italy-Trieste	2 252 (11.5)	-0.71 (0.03)
Italy-Verona	4 569 (23.3)	-0.19 (0.01)
Romania-Multicenter	67 (0.3)	-0.85 (0.08)
Slovakia-Multicenter	584 (3.0)	-0.84 (0.05)
Spain-Barcelona	524 (2.7)	0.32 (0.07)
Spain-Oviedo	33 (0.2)	-0.78 (0.13)
Sex		
Male	5 319 (27.4)	-0.28 (0.01)
Female	14 103 (72.6)	-0.31 (0.01)
Age		
≤ 29	2 269 (11.6)	-0.36 (0.01)
30-39	4 294 (21.9)	-0.36 (0.01)
40-49	4 722 (24.1)	-0.33 (0.01)
≥ 50	8 330 (42.5)	-0.24 (0.01)
Job title		
Administration	1 569 (8.1)	-0.25 (0.03)
Physician (including residents)	4 989 (25.7)	-0.27 (0.01)
Nurse	7 312 (37.7)	-0.33 (0.01)
Technician	1 622 (8.4)	-0.25 (0.03)
Other HCW (including auxiliary workers)	3 876 (20.0)	-0.34 (0.02)
Previous Covid-19 infection (PCR/Antigen)		
Never infected	16 824 (85.8)	-0.30 (0.01)
Infected before first serological measurement	2 385 (12.2)	-0.62 (0.02)
Infected between first and second serological measurement	379 (1.9)	1.00 (0.07)
Infected at both times	27 (0.2)	0.96 (0.29)
Number of doses		
2 doses	18 437 (94.0)	-0.28 (0.01)
3 doses	1 178 (6.0)	0.93 (0.04)
Time between first & second serological measures		
< 30d	13 (0.1)	0.74 (0.77)
30d-60d	175 (0.9)	-0.36 (0.06)
60d-90d	668 (3.4)	-0.36 (0.03)
90d-120d	3 200 (16.3)	-0.31 (0.01)
120d-150d	5 574 (28.4)	-0.36 (0.01)
150d-180d	1 840 (9.4)	-0.49 (0.02)
180d-210d	4 894 (24.9)	-0.45 (0.02)

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210d-240d	1 824 (9.3)	-0.30 (0.03)
240d-270d	618 (3.1)	0.22 (0.06)
270d-300d	426 (2.2)	0.95 (0.07)
300d-330d	276 (1.4)	0.99 (0.08)
330d-360d	71 (0.4)	0.68 (0.15)
360d-390d	19 (0.1)	1.25 (0.21)
390d-410d	14 (0.1)	1.51 (0.32)
410d-440d	3 (0.0)	3.10 (.)
Time between first serological measure & first dose of vaccine		
<90d	10 202 (52.0)	-0.30 (0.01)
>=90d	9 413 (48.0)	-0.32 (0.01)

SE, standard error

Most of the study population consisted of women (72.6%), and a large proportion of subjects were >=50 years old (42.5%). The HCW were mostly nurses (37.7%) and physicians (25.7%). Overall, 85.8% had no previous COVID-19 infection; the large majority (94.0%) were administered with 2 doses of COVID-19 vaccine, while 1,178 HCW (6.0%) from the cohorts of Bari, Bologna, Romania, Slovakia, Barcelona and Oviedo received a third dose. Time between two consecutive serological measures ranged from less than 30 days and 440 days, with 16.3% being performed between 90 and 120 days, 28.4% between 120 and 150 days, 9.4% between 150 and 180 days, 24.9% between 180 and 210 days and 9.3% between 210 and 240 days. We distinguished the serologies based on whether they were collected before 90 days or >=90 days from the first dose of COVID-19 vaccine (52.0% vs 48.0%). The large majority of subjects with 2 doses (98.2%) received Comirnaty, followed by Spikevax and other and mixed vaccines (not shown in detail).

When calculating the mean serology difference between two measurements, we observed some difference by study center, with Bari and Barcelona showing significant positive coefficient. This was mainly explained by the fact that several second blood samples in these cohorts were collected in the days following the third dose. **Figure 1** illustrates the average timing of serological measurements by study center. As the knots contain the average number of days between first and second serology, last serology appears not to be often performed after the booster vaccine dose, and samples were collected in quite different points in time in each center. On the other hand, vaccinations were administered mostly with the same timing, with about 30 days between first and second dose and around the booster dose being administered around 300 days after first vaccination.

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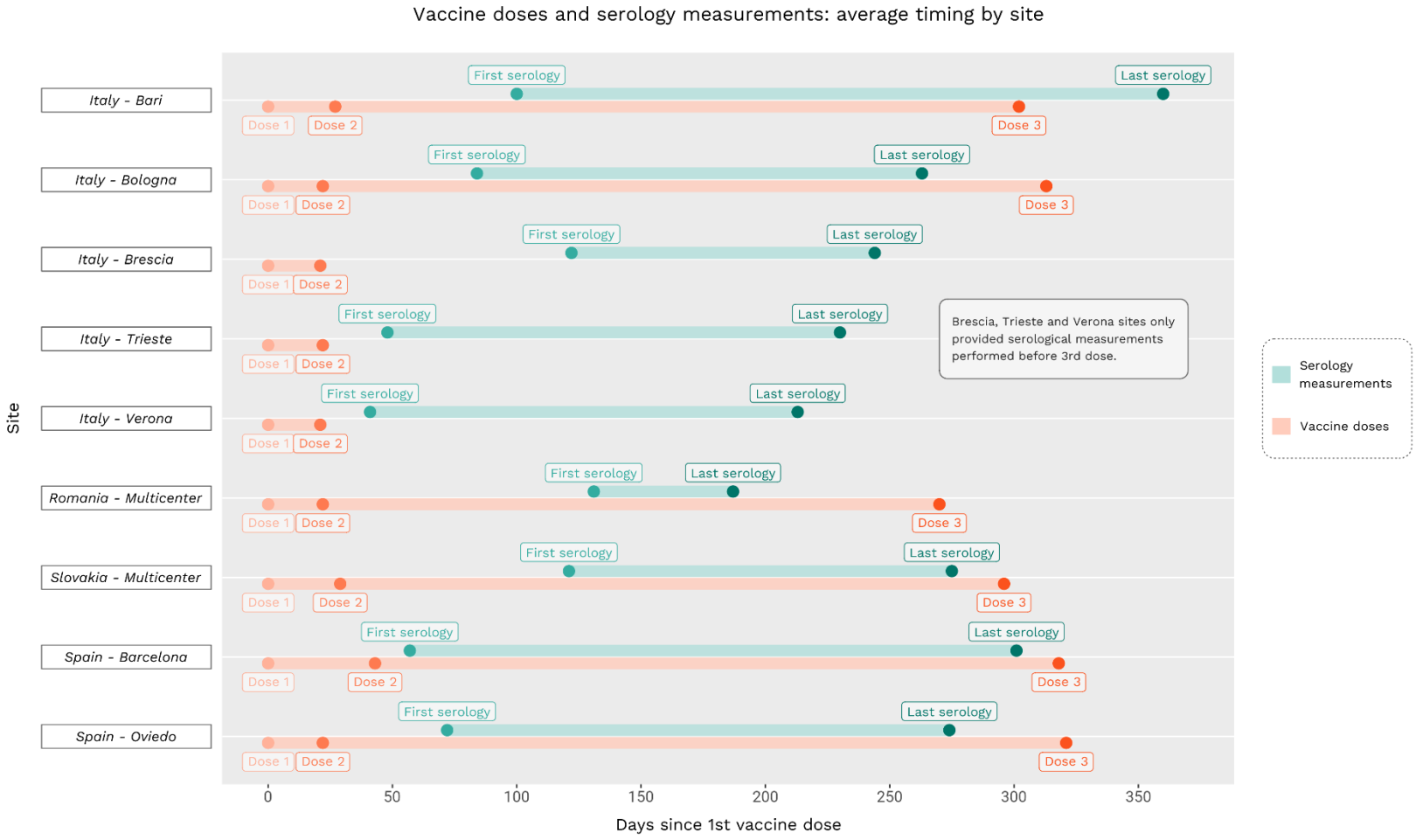
Figure 1. Timing of vaccination and serological measurements by cohort



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According to the time between the two serological samples, we calculated a progressively reduced difference from <30 days to 210-240 days (ranging among 0.74 and -0.30 SE), and a following increased difference until days 410-440 (from 0.22 to 3.10 SE). No substantial difference was found by time (< or >=90 days) between first serology and first vaccination (-0.30 and -0.32 SE).

The main results of the multivariate regression are also presented in Table 2. Results are expressed as relative risk of having an absolute difference of one standard error of the cohort-specific distribution between the second and the first serological measurement. Among HW with two vaccine doses, the difference was negative (decrease in serological level), as a consequence RRs greater than one correspond to a larger decrease in serological level between the second and the first measurement, and vice-versa. Among subjects with three vaccines dose, the difference between the second and the first dose was positive (increase in antibody level), and RRs greater than one correspond to a larger increase in the difference between the two tests.

The overall results shown in **Table 2** are dominated by HCW with two vaccine doses. Compared to Bologna, the centers of Bari, Trieste, Verona, Romania, Slovakia and Barcelona registered a significant smaller difference in the antibodies level from first to second blood sample. Women were slightly more likely to experience an increase in the difference between serological measurements, while age was associated with a decreased difference. No difference was found by job title.

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Table 2. Multivariate analysis of determinants of difference between second and first serological measurement

VARIABLE	RR	P-VALUE	95% CI
Cohort			
Italy-Bari	0.30	0.000	0.25, 0.37
Italy-Bologna	ref		
Italy-Brescia	0.95	0.001	0.91, 0.98
Italy-Trieste	0.39	0.000	0.37, 0.42
Italy-Verona	0.58	0.000	0.55, 0.61
Romania-Multicenter	0.54	0.000	0.47, 0.62
Slovakia-Multicenter	0.34	0.000	0.31, 0.37
Spain-Barcelona	0.47	0.000	0.43, 0.52
Spain-Oviedo	1.09	0.658	0.73, 1.63
Sex	-	-	
Male	ref		
Female	1.02	0.048	1.00, 1.04
Age	-	-	
10 years increase	0.97	0.000	0.96, 0.98
Job title	-	-	
Administration	ref		
Physician (including residents)	0.98	0.438	0.95, 1.02
Nurse	0.98	0.411	0.95, 1.02
Technician	1.01	0.760	0.96, 1.05
Other HCW (including auxiliary workers)	0.99	0.626	0.95, 1.03
Previous Covid-19 infection	-	-	
Never infected	ref		
Infected before the first serological measurement	1.24	0.000	1.19, 1.29
Infected between the two serological measurements	2.90	0.000	2.52, 3.34
Infected at both times	1.37	0.070	0.97, 1.93
Number of doses	-	-	
2 doses	ref		
3 doses	4.27	0.000	3.99, 4.58
Time between first vaccine dose & first serology measure	-	-	
30 days increase	0.92	0.000	0.91, 0.94
Time between first serology measure and second serology measure	-	-	
30 days increase	0.96	0.000	0.95, 0.97
Standardized result of first serological measurement	-	-	
1 SD increase in ln(AB)	0.62	0.000	0.61, 0.64

Outcome variable is absolute value of difference between last and first serology (standardized values). Models include terms for cohort, sex, age (10 days increase), job title, number of vaccine doses received, previous COVID-19 infection, time difference between first serology measure and first dose of vaccine (30 days increase), time difference between first serology measure and second serology measure (30 days increase), standardized result of first serological measurement
RR, relative risk; SE, standard error; CI, confidence interval; Ref, reference category

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When considering previous COVID-19 infection, the HCW who got infected between the two serological measurements had a RR of 3.53 (95% CI=3.02-4.13) compared to the never infected. Those infected before the first serological measurement resulted to have 1.22 positive difference in serologies (95% CI=1.17-1.28). The 30-days increase in time between first vaccine dose and first serology correlated with the detection of a slight negative difference in the serological samples (RR 0.91, 95% CI=0.90-0.92), as well as time in between the two samples (RR 0.95, 95% CI 0.94-0.96).

When the model was additionally adjusted by type of vaccine the results were substantially overlapping. Compared to Comirnaty, Spikevax resulted to be associated to positive difference in the two serologies (RR 1.20, 95% CI=1.08-1.34). The administration of other types of vaccines showed similar results, despite being impaired by small numbers.

Tables 3 and **4** illustrate the results of the analysis restricted to HCW administered with 2 and 3 doses of vaccine, respectively. Results in Table 3 are similar to those of the overall analysis, since most HCW included in the analysis received two vaccine doses. Among 1,168 HCW from Bari, Bologna, Slovakia, Barcelona, and Oviedo with three vaccine doses (Table 4), female sex had a negative difference in serological level (RR 0.91, 95% CI 0.83-0.99) while age was related to a 5% positive increase (95% CI=1.01-1.08). No significant difference was found by job title, while HCW who got infected before the first serological measurement went through a negative difference in the serological levels (RR 0.82, 95% CI=0.71-0.95) compared to those never infected. The 30 days increase between first vaccine dose and first serology, and that between first and second serology measurements, were related to 18% and 17% increased difference respectively ($p<0.001$).

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***Table 3**. Multivariate analysis of determinants of difference between second and first serological measurement – Subjects with two vaccine doses*

VARIABLE	RR	P-VALUE	95% CI
Cohort			
Italy-Bari	0.74	0.063	0.54, 1.02
Italy-Bologna	Ref		
Italy-Brescia	1.00	0.862	0.97, 1.04
Italy-Trieste	0.42	0.000	0.39, 0.44
Italy-Verona	0.60	0.000	0.57, 0.64
Romania-Multicenter	0.46	0.000	0.39, 0.55
Slovakia-Multicenter	0.39	0.000	0.36, 0.43
Spain-Barcelona	0.56	0.000	0.50, 0.62
Spain-Oviedo	1.10	0.652	0.73, 1.66
Sex	-	-	
Male	ref		
Female	1.03	0.006	1.01, 1.05
Age	-	-	
10 years increase	0.96	0.000	0.95, 0.97
Job title	-	-	
Administration	ref		
Physician (including residents)	1.00	0.970	0.96, 1.04
Nurse	0.99	0.651	0.96, 1.03
Technician	1.01	0.545	0.97, 1.06
Other HCW (including auxiliary workers)	0.99	0.518	0.95, 1.03
Previous Covid-19 infection	-	-	
Never infected	ref		
Infected before the first serological measurement	1.22	0.000	1.17, 1.28
Infected between the two serological measurements	3.54	0.000	3.02, 4.14
Infected at both times	1.67	0.058	0.98, 2.83
Time between first vaccine dose & first serology measure	-	-	
30 days increase	0.91	0.000	0.90, 0.92
Time between first serology measure and second serology measure	-	-	
30 days increase	0.95	0.000	0.94, 0.96
Standardized result of first serological measurement	-	-	
1 SD increase in ln(AB)	0.64	0.000	0.62, 0.66
Type of vaccine			
Pfizer	Ref		
Moderna	1.20	0.001	1.08, 1.34
Other & Mixed vaccines	1.34	0.051	1.00, 1.80

Outcome variable is absolute value of difference between last and first serology (standardized values). Models include terms for cohort, sex, age (10 days increase), job title, number of vaccine doses received, previous COVID-19 infection, time difference between first serology measure and first dose of vaccine (30 days increase), time difference between first serology measure and second serology measure (30 days increase), standardized result of first serological measurement; type of vaccine

RR. relative risk; SE, standard error; CI, confidence interval; Ref, reference category

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***Table 4**. Multivariate analysis of determinants of difference between second and first serological measurement – Subjects with three vaccine doses*

VARIABLE	RR	P-VALUE	95% CI
Cohort			
Italy-Bari	0.29	0.000	0.22, 0.38
Italy-Bologna	Ref		
Slovakia-Multicenter	0.09	0.000	0.06, 0.13
Spain-Barcelona	0.24	0.000	0.18, 0.32
Spain-Oviedo	2.11	0.000	1.79, 2.49
Sex	-	-	
Male	ref		
Female	0.91	0.034	0.83, 0.99
Age	-	-	
10 years increase	1.05	0.012	1.01, 1.08
Job title	-	-	
Administration	ref		
Physician (including residents)	0.91	0.193	0.79, 1.05
Nurse	0.91	0.198	0.80, 1.05
Technician	0.88	0.190	0.72, 1.07
Other HCW (including auxiliary workers)	0.96	0.658	0.82, 1.13
Previous Covid-19 infection	-	-	
Never infected	ref		
Infected before the first serological measurement	0.82	0.009	0.71, 0.95
Infected between the two serological measurements	0.98	0.670	0.88, 1.09
Infected at both times	0.92	0.542	0.71, 1.20
Time between first vaccine dose & first serology measure	-	-	
30 days increase	1.18	0.000	1.12, 1.25
Time between first serology measure and second serology measure	-	-	
30 days increase	1.17	0.000	1.12, 1.23
Standardized result of first serological measurement	-	-	
1 SD increase in ln(AB)	0.47	0.000	0.41, 0.54

Outcome variable is absolute value of difference between last and first serology (standardized values). Models include terms for cohort, sex, age (10 days increase), job title, number of vaccine doses received, previous COVID-19 infection, time difference between first serology measure and first dose of vaccine (30 days increase), time difference between first serology measure and second serology measure (30 days increase), standardized result of first serological measurement
RR, relative risk; SE, standard error; CI, confidence interval; Ref, reference category

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Conclusions

The present study shows and quantifies the difference in serological levels occurred between the first and the second measurement after COVID-19 vaccination in a large European sample of HCW. A decrease in the antibodies level was reported in every center, except from Bari and Barcelona. Small difference was observed by sex and age- with men and older subjects undergoing a wider decrease of the antibodies, as well as by job title. The main driver of a positive difference in the two serological samples was previous COVID-19 infection. On the other hand, the more days in between the first vaccination and the first serological sample, and the deeper the negative difference between the second and the first antibodies levels. Increasing days in between the two samplings was also a determinant of higher negative difference in the antibody's levels detected.

Recommendations

The pooled ORCHESTRA cohort of HCW represents a unique tool to investigate the patterns and determinants of antibody response following COVID-19 vaccination. Additional analyses with long follow-up and multiple tests for individual HCW should be conducted.

Additional further studies are warranted in other populations to further describe temporal changes in serological levels after COVID-19 vaccination, as well as to clarify the role of different types of vaccines and timing of infection.

In general, in order to better address the pandemic situation and manage vaccination strategy at both the occupational and population-based level, studies focused on the protectiveness of vaccination-driven antibodies are needed.

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