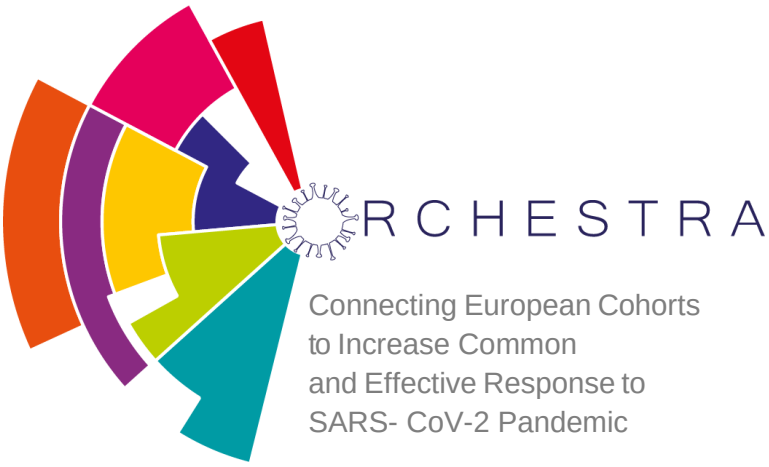

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Final analysis of serology results after vaccination

UNIBO

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Executive summary

The duration of immune response to COVID-19 vaccination is of major interest. Our aim was to analyze the determinants of anti-SARS-CoV-2 IgG titer at 6 months after 2-dose vaccination in an international cohort of vaccinated healthcare workers (HCWs). We analyzed data on levels of anti-SARS-CoV-2 Spike antibodies and sociodemographic and clinical characteristics of 6,327 vaccinated HCWs from 8 centers from Germany, Italy, Romania and Slovakia. Time between 1st dose and serology ranged 150-210 days. Serological levels were log-transformed to account for the skewness of the distribution and normalized by dividing them by center-specific standard errors. We fitted center-specific multivariate regression models to estimate the cohort-specific relative risks (RR) of an increase of 1 standard deviation of log antibody level and corresponding 95% confidence interval (CI), and finally combined them in random-effects meta-analyses. A 6-month serological response was detected in 99.6% of HCWs. Female sex (RR 1.10, 95%CI 1.00-1.21), past infection (RR 2.26, 95%CI 1.73-2.95) and two vaccine doses (RR 1.50, 95%CI 1.22-1.84) predicted higher IgG titer, contrary to interval since last dose (RR for 10-day increase 0.94, 95%CI 0.91-0.97) and age (RR for 10-year increase 0.87, 95%CI 0.83-0.92). M-RNA-based vaccines ($p<0.001$) and heterologous vaccination (RR 2.46, 95%CI 1.87-3.24, one cohort) were associated with increased antibody levels. Female gender, young age, past infection, two vaccine doses, and m-RNA and heterologous vaccination predicted higher antibody level at 6 months. These results need to be confirmed in independent cohorts and compared with trends observed with longer follow-ups.

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Abbreviations

AIFA, Italian Medicine Agency

BMI, body mass index

CI, confidence interval

HCW, Healthcare worker

INMI, Italian National Institute of Infectious Diseases

RR, relative risk

SD, standard deviation

SE, standard error

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Introduction

COVID-19 represents one of the major acute infectious threats of the XXI century. The pandemic nature of COVID-19 infection rose several challenges, leading to deep daily life changes in most populations of the world [1]. The pandemic implied an urgent need for vaccines development, which first entered in use in December 2020 [2]. The mRNA mechanism of newly developed vaccines, namely Comirnaty (BioNTech/Pfizer) and Spikevax (Moderna), has been largely debated. mRNA vaccines were known to be versatile and rapid to design even before COVID pandemic [3], with the benefit of a short manufacturing time matched with high efficacy, and to be overall safe [4]. In many countries, health care workers (HCW) were among the first population groups to be recommended the vaccination, given their high exposure to COVID-19 infection [5].

Once vaccines were recommended at mass level against infection spreading [6], one of the main issues became to determine their effectiveness against COVID-19 infection. Preliminary data showed that vaccines were effective against the development of symptoms and reduced the risk of infection [2,4,7]. Indeed, immune responsiveness is necessary for a vaccine to be effective towards its target [8]. The quantity of antibodies against the targeted microorganism depends on the type of vaccine and can be interpreted as an index of effectiveness of a vaccine, and the type of induced antibodies [9].

To date, few studies have evaluated the longitudinal immune response to COVID-19 vaccines [10-13]. A recent publication reviewed the available data on duration of vaccine effectiveness, which was assessed to decrease by about 20-30% within 6 months [14].

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Methods

ORCHESTRA comprises a prospective multicenter cohort of HCWs employed in hospitals in multiple countries [15] including over 60,000 HCWs. This analysis includes HCWs from one center in Germany (Munich), 5 centers in Italy (Bari, Bologna, Brescia, Trieste and Verona), as well as in several centers in Romania and Slovakia (the two latter treated as individual cohorts), with serological results at 6 months after first vaccination dose. Data on sociodemographic characteristics, results of PCR testing, and vaccination status, including date of vaccination doses and type, were either abstracted from medical surveillance records or collected using questionnaires or ongoing loco-regional databases. Results on level of anti-S antibodies were either collected from medical records or generated through ad-hoc testing. All cohorts included in the ORCHESTRA project have undergone extensive data harmonization.

The proportion of HCWs who did not develop a serological response after vaccination varied across the cohorts from 0% to 1.1%; these subjects were excluded from all analysis on serological results. The present analysis comprises 6,327 HCWs with available and positive serology results during a 6-month timeframe from 1^{rst} dose administration, defined as the interval 150-210 days (**Table 1**).

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Table 1. Selected characteristics of the cohorts of HCW included in the analysis

Cohort	Sources of HCW	Source of data	Time period – vaccination
Germany-Munich	München Klinik Group, Hospital Barmherzige Brüder in München	Questionnaire and DBS data at recruitment	December 2020 – March 2021
Italy-Bari	University Hospital of Bari	Health surveillance records	December 2020 – March 2021
Italy-Bologna	Public hospitals and public health authority of Bologna	Health surveillance records	December 2020 – March 2021
Italy-Brescia	Public hospitals and public health authority of Brescia	Health surveillance records	February-May 2021
Italy-Trieste	University Hospital of Trieste	Health surveillance records	January – March 2021
Italy-Verona	University Hospital of Verona	Health surveillance records; ongoing regional databases	December 2020 – April 2021
Romania-Multicenter	Public health authority and institutes, medical offices, hospitals	Active recruitment	January - March 2021 (85%)
Slovakia-Multicenter	Hospitals, outpatient clinics, public health authority, social care units	Active recruitment	January – March 2021 (98%)

HCW, healthcare worker

The primary outcome of this analysis was level of serum antibodies at six months. Methods of measurement of antibody level varied across centers and time periods; details are reported in **Table 2**.

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Table 2. Analytical methods used to measure SARS-CoV-2 antibody level.

Cohort	Type of serology test	Mean (SD) of serological level*	Mean (SD) of standardized serological level*†
Germany- Munich	Roche Elecsys ® anti SARS CoV2 S -	47.35 (2.68)	3.72 (0.06)
Italy-Bari	Abbot SARS-COV-2 IgG II Quant test	1711.04 (252.94)	8.45 (0.13)
Italy-Bologna	Ab anti SARS CoV-2 S (RBD) IgG ECLIA	1062.70 (17.96)	7.38 (0.02)
Italy-Brescia	Roche Elecsys® anti SARS CoV2 S	2349.10 (162.77)	6.07 (0.06)
Italy-Trieste	CMIA anti S1-RBD	3383.6 (471.98)	6.15 (0.06)
Italy-Verona	CLIA trimeric S IgG	868.39 (39.53)	6.39 (0.02)
Romania- Multicenter	Abbot SARS-COV-2 IgG II Quant test	1702.06 (3674.69)	6.35 (0.99)
Slovakia- Multicenter	QuantiVac ELISA (IgG) EUROIMMUN	904.82 (95.23)	8.58 (0.19)

** Adjusted by age, according to the Standard European Population*
† Standardized according to the formula: ln(AB) / sd[ln(AB)], where AB stands for antibody level.

We conducted a two-stage analysis. In the first stage, we executed descriptive analysis of the outcome and explanatory variables. For quantitative analyses antibody levels were log-transformed to account for the skewness of the distribution. To take into account the heterogeneity in analytical methods, log- transformed results were normalized by dividing them by the center-specific standard errors. We fitted multivariate linear regression models to estimate cohort-specific relative risks (RR) and corresponding 95% confidence intervals (CI) of an increase of one standard deviation (SD) of normalized log- transformed antibody level. Multivariate regression models, both logistic and linear, comprised sex, age, and potential determinants of levels of antibodies, including job title (technician, nurse, physician, other HCWs vs administrative personnel), time since last dose of COVID vaccine, COVID infection prior to serology (either before or after vaccination), previous positive anti-N serology (both in qualitative and quantitative terms), number of vaccine doses, type of vaccine, and body mass index (BMI).

In a second phase, cohort-specific results were combined using random-effects meta-analyses [16]; heterogeneity between cohort-specific results was tested using the I^2 method [17]. Secondary analyses on vaccine type were restricted to the cohorts from Bologna and Munich. Stata®

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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. Each cohort was approved by the local ethical board.

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Results

A total of 6,327 vaccinated HCWs from 8 European cohorts were included in the analysis. Selected characteristics of these HCWs are described in **Table 3**. Subjects were mostly women, with proportion ranging from 58.1% (Bari) to 81.4% (Slovakia and Romania), and older than 50 years old (from 36.8% in Bologna to 57.1% in Romania). The most frequent job titles were nurse and physician in all the cohorts, except for Slovakia where the largest category was that of other HCWs. The proportion of HCWs with a confirmed COVID-19 infection (positive by either PCR or anti-N antibodies) prior to the blood sampling was quite heterogeneous, ranging between 1.35 (Bari) to 24.1% (Brescia). Qualitative data on pre- vaccination serology were available for 5 out of 8 cohorts and showed differences among the study centers, with proportions of negative serology ranging from 51.8% (Brescia) to 90.5% (Bari). When considering type of vaccine, Comirnaty was the most commonly administered vaccine everywhere, representing 100% of the vaccinations in Bari, Verona and Trieste. Munich was the only center where a sizable proportion of subjects received other vaccines, including combinations.

Overall, 199 HCWs (3.2%) received only one dose of vaccine. This proportion was largest in Brescia (17.4%). Instead, 100% of the subjects from Bari, Slovakia and Romania cohorts completed the two-dose vaccination course. Pre-vaccination anti-N antibody level was provided by 4 cohorts and the intervals varied by cohort (**Table 3)**. The mean timeframe between first vaccine dose and blood sample varied between 161.0 (Slovakia) to 203.3 days (Bari), and the overall mean was 185.1, within the predefined range of 150-210 days.

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Table 3. Selected characteristics of HCWs included in the analysis

	Germany-Munich (%)	Italy-Bari (%)	Italy-Bologna (%)	Italy-Brescia (%)	Italy-Trieste (%)	Italy-Verona (%)	Romania-Multicenter (%)	Slovakia-Multicenter (%)
Number of HCW	292	74	2,833	253	526	2,062	210	95
Qualitative characteristics [+]								
Sex								
Men	83 (28.42)	31 (41.9)	785 (27.7)	57 (22.5)	127 (26.8)	508 (24.6)	39 (18.6)	18 (18.9)
Women	209 (71.6)	43 (58.1)	2,048 (72.3)	196 (77.5)	347 (73.2)	1,554 (75.4)	171 (81.4)	77 (81.4)
Age group								
<= 29	64 (21.92)	13 (17.6)	421 (14.9)	47 (18.6)	31 (6.5)	285 (13.8)	10 (4.8)	11 (11.6)
30 – 39	54 (18.49)	11 (14.9)	709 (25.0)	37 (14.6)	70 (14.8)	412 (20.0)	19 (9.0)	11 (11.6)
40 – 49	48 (16.44)	15 (20.3)	659 (23.3)	59 (23.3)	126 (26.6)	448 (21.7)	61 (29.1)	24 (25.3)
>= 50	126 (43.15)	35 (47.3)	1,044 (36.8)	110 (43.5)	247 (52.1)	917 (44.5)	120 (57.1)	49 (51.6)
Job title								
Administration	NA	3 (4.4)	103 (3.6)	32 (12.6)	19 (4.0)	211 (10.2)	23 (10.9)	17 (17.9)
Physician	NA	33 (48.5)	621 (22.0)	49 (19.4)	54 (11.3)	480 (23.3)	93 (44.3)	11 (11.6)
Nurse	NA	19 (27.9)	1,119 (39.6)	84 (33.2)	203 (42.6)	806 (39.1)	29 (13.8)	20 (21.0)
Technician	NA	\	273 (9.7)	20 (7.9)	26 (5.5)	233 (11.3)	58 (27.6)	13 (13.7)
Other HCW	NA	13 (19.1)	709 (25.1)	68 (26.9)	174 (36.6)	332 (16.1)	7 (3.3)	34 (35.8)
Previous Covid-19 infection **								
No	262 (90.97)	73 (98.6)	2,609 (92.1)	192 (75.9)	432 (82.1)	1,752 (85.0)	182 (86.7)	81 (85.3)
Yes	26 (9.03)	1 (1.3)	224 (7.9)	61 (24.1)	94 (17.9)	310 (15.0)	28 (13.3)	14 (14.7)
Qualitative pre-vaccination serology								
Negative	NA	67 (90.5)	1,045 (88.1)	29 (51.8)	142 (69.3)	1,526 (89.5)	NA	NA
Positive	NA	7 (9.5)	141 (11.9)	27 (48.2)	63 (30.7)	179 (10.5)	NA	NA

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Table 3 (cont'd)

Type of vaccine								
Comirnaty	198 (70.4)	74 (100.0)	2,732 (97.3)	247 (97.6)	526 (100.0)	2,062 (100.0)	206 (98.1)	94 (98.9)
Spikevax	24 (8.54)	0 (0.0)	74 (2.6)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)
Vaxzevria	11 (3.91)	0 (0.0)	3 (0.1)	5 (2.0)	0 (0.0)	0 (0.0)	2 (0.9)	1 (1.0)
Vaxzevria + Comirnaty	45 (16.01)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vaxzevria + Spikevax	3 (1.07)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of doses								
1 dose received	11 (3.77)	0 (0.0)	18 (0.6)	44 (17.4)	34 (6.5)	92 (4.5)	0 (0.0)	0 (0.0)
2 doses received	281 (96.23)	74 (100.0)	2,815 (99.4)	209 (82.6)	492 (93.5)	1,970 (95.5)	210 (100.0)	95 (100.0)
Quantitative characteristics *								
Standardized quantitative serology at 6-month								
Mean (SD)	3.72 (0.06)	8.40 (0.12)	7.31 (0.02)	6.02 (0.06)	6.29 (1.00)	6.51 (1.00)	6.32 (0.99)	8.51 (0.10)
Quantitative pre-vaccination serology								
Mean (SD)	NA	92.0 (605.8)	\	44.0 (66.9)	29.9 (75.9)	0.9 (3.7)	NA	NA
Standardized quantitative pre-vaccination serology								
Mean (SD)	NA	0.55 (1.00)	\	0.30 (1.38)	4.23 (1.00)	-1.11 (1.00)	NA	NA
Days between pre-vaccination serology and serology at 6-month								
Mean (SD)	NA	204 (7)	361 (101)	300 (28)	422 (129)	295 (48)	NA	NA
Range	NA	186-254	155-626	200-329	157-628	182-494	NA	NA
Days between 1st dose and serology at 6-month								
Mean (SD)	179 (17)	203 (2)	177 (18)	185 (15)	173 (19)	199 (13)	197 (13)	161 (16)
Range	150-210	194-208	150-210	150-210	150-210	151-210	154-210	150-209

+, Frequency and percentage for the categorical variables are reported.

**, Mean and SD for the continuous variables are reported. NA, no data available.*

*** In Germany-Munich cohort, previous Covid-19 infection has been detected by at least one positive PCR or Anti-N.*

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Table 4 illustrates the serology level distribution categorized by sex, age and cohort.

Table 4. Standardized serology level distribution by cohort, sex and age

Variable	Standardized. quantitative serology level – Mean (SD)							
	Germany-Munich	Italy-Bari	Italy-Bologna	Italy-Brescia	Italy-Trieste	Italy-Verona	Romania-Multicenter	Slovakia-Multicenter
Sex*	-	-	-	-	-	-	-	-
Male	3.60 (0.10)	8.37 (0.19)	7.29 (0.04)	6.12 (0.13)	6.10 (0.12)	6.35 (0.04)	6.07 (0.81)	8.42 (0.46)
Female	3.83 (0.07)	8.52 (0.17)	7.41 (0.02)	6.06 (0.07)	6.15 (0.08)	6.40 (0.03)	6.41 (1.03)	8.59 (0.21)
Age (yrs)	-		-	-	-	-	-	-
≤ 29	4.05 (0.09)	8.77 (0.30)	7.74 (0.04)	6.30 (0.12)	6.52 (0.17)	6.62 (0.04)	6.46 (0.54)	8.70 (0.33)
30-39	3.70 (0.18)	8.42 (0.15)	7.48 (0.03)	5.82 (0.17)	6.17 (0.12)	6.41 (0.04)	6.16 (0.95)	8.41 (0.20)
40-49	3.51 (0.13)	8.81 (0.23)	7.17 (0.03)	5.89 (0.13)	6.00 (0.08)	6.22 (0.04)	6.32 (1.04)	8.45 (0.18)
≥ 50	3.62 (0.09)	8.08 (0.18)	7.12 (0.03)	6.04 (0.10)	5.86 (0.07)	6.25 (0.03)	6.33 (1.02)	8.52 (0.16)

** Adjusted by age, according to the Standard European Population.*

The results of the meta-analysis for the determinants of serology response at 6 months are reported in **Table 5.**

Overall, women were more likely to develop a higher antibody level than men (RR of an increase of one SD of normalized log-transformed antibody level 1.10, 95% CI 1.00-1.21, p-heterogeneity 0.1). Cohort-specific RRs ranged from 0.91 to 1.51.

Ageing was inversely related to serologic response in all the cohorts, with RR=0.87 for a 10-year increase in age (95% CI 0.83-.92, p-heterogeneity 0.003). Cohort-specific RRs were all below 1 and ranged from 0.76 to 0.98. Job title (seven cohorts) was not associated to the serology level, either in the meta-analysis or in cohort-specific analyses (details not shown).

We found a RR of 2.26 (95% CI 1.73-2.95, p-heterogeneity < 0.001, all eight cohorts) for previous COVID-19 infection; cohort-specific RRs ranged from 1.01 to 4.95. A RR of 1.50 (95% CI 1.22-1.84, five cohorts) was detected for two vs one dose of vaccine. A 10-day increase since last dose (seven cohorts) showed significant probability of lower level of antibodies (RR 0.94, 95% CI=0.91-0.97).

Viral-vector vaccines (four cohorts) resulted in a non-significant lower probability of increased serological response (RR 0.58; 95% CI=0.27-1.23). HCWs who had a positive or higher serology

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Table 5. Determinants of standardized antibody level at 6-month

	RR	95% CI	p-value
Gender* [all]			
Men	1 (Ref)		
Women	1.10	1.00- 1.21	0.041
Age* [all]			
10 years increase	0.87	0.83-0.92	<0.001
Job title* [It-Ba, It-Bo, It-Br, It-Ts, It-Vr, Ro-Mc, Sk-Mc]			
Administration	1 (Ref)		
Physician	1.00	0.89-1.13	0.990
Nurse	0.93	0.81-1.07	0.302
Technician	1.04	0.92-1.18	0.495
Other HCW	1.03	0.91-1.16	0.690
Previous Covid-19 infection* [all]			
No	1 (Ref)		
Yes	2.26	1.73-2.95	<0.001
Number of doses* [Ge-Mu, It-Bo, It-Br, It-Ts, It-Vr]			
1 dose received	1 (Ref)		
2 doses received	1.50	1.22-1.84	<0.001
Days between last dose and serology at 6-month* [It-Ba, It-Bo, It-Br, It-Ts, It-Vr, Ro-Mc, Sk-Mc]			
10 days increase	0.94	0.91-0.97	<0.001
Type of vaccine* [Ge-Mu, It-Bo, It-Br, Ro-Mc]			
mRNA	1 (Ref)		
Viral vector	0.58	0.27-1.23	0.154
Qualitative pre-vaccination serology* [It-Ba, It-Bo, It-Br, It-Ts, It-Vr]			
Negative	1 (Ref)		
Positive	1.85	1.35-2.52	<0.001
Standardized quantitative pre-vaccination serology* [It-Ba, It-Br, It-Ts, It-Vr]			
1 SD increase in ln(AB)	1.19	1.05-1.35	0.006
Days between pre- vaccination serology and serology at 6-month† [It-Ba, It-Br, It-Ts, It-Vr]			
30 days increase	1.09	0.97-1.23	0.129
BMI* [Ro-Mc, Sk-Mc]			
1 unit increase	1.02	0.99-1.04	0.186

Ge-Mu, Germany-Munich; It-Ba, Italy-Bari; It-Bo, Italy-Bologna; It-Br, Italy-Brescia; It-Ts, Italy- Trieste; It-Vr, Italy-Verona; Ro-Mc, Romania-Multicenter; Sk-Mc, Slovakia-Multicenter;

RR, relative risk; CI, confidence interval; BMI, body mass index; Ref, reference category

** Adjusted by age, gender, job title previous Covid-19 infection, number of doses and days between last dose and serology at 6-month (excluding variable itself)*

† Adjusted by age, gender, job title, previous Covid-19 infection, number of doses, and standardized quantitative pre-vaccination serology

level before vaccination had significantly a higher probability on an increased level respectively (RR=1.85, 95% CI=1.35-2.52) and (RR=1.19, 95% CI=1.05-1.35). No difference was found based on 30 days increase in the interval since pre-vaccination serology (four cohorts): results were quite inconsistent between the cohorts. When the analysis was stratified by both infection and vaccination status, HCWs reporting history of COVID infection and administered with two

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doses had higher antibodies than those with no infection and one only dose (RR=23.41, 95% CI=0.46-1194.51, based on 5 cohorts). No relation was found with increasing BMI based on Slovakia and Romania cohorts.

We performed separate analyses within single centers with available data on different vaccine types, namely Italy-Bologna and Germany-Munich (**Table 6**). When comparing the different vaccines in the Italy-Bologna cohort, a higher immunogenicity was found for Spikevax against Comirnaty, up to a RR of 2.05 (p<0.001). Vaxzevria (n=74) resulted to be associated to higher level of antibodies too, but without significance (RR=1.62, p=0.31); this latter result is hampered by the very small number of HCWs receiving this vaccine (n=3). The analysis of the Germany-Munich cohort provided slightly different results from that of Bologna: Spikevax was not significantly associate to a quantitative immune response (RR=1.23, p=0.13); Vaxzevria was less able to induce serological response (RR=0.50, p=0.019).

Table 6. Relative risk for type of vaccine

Cohort; type of vaccine	RR	95% CI	p-value
Germany, Munich			
Comirnaty	1 (Ref)	-	
Spikevax	1.23	[0.85, 1.77]	0.1
Vaxzevria	0.50	[0.28, 0.89]	0.02
Vaxzevria + Comirnaty	2.35	[1.75, 3.14]	<0.001
Vaxzevria + Spikevax	2.05	[1.14, 3.71]	0.02
Italy, Bologna			
Comirnaty	1 (Ref)	-	
Spikevax	2.05	[1.61, 2.60]	<0.001
Vaxzevria	1.62	[0.63, 4.16]	0.3

RR, relative risk adjusted by sex, age, job title, time since 1st dose, previous Covid-19 infection and number of doses; CI, confidence interval; Ref, reference category

Compared to homologous Comirnaty vaccination, heterologous vaccination with Vaxzevria & Comirnaty and that with Vaxzevria & Spikevax were significantly more likely to produce higher immune response, with RR of 2.35 (p<0.001) and 2.05 (p=0.017) respectively, with an overall RR for heterologous vs. homologous vaccination equal to 2.46 (95% CI 1.87-3.24).

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Conclusions

We analyzed consecutive serologies of more than 6400 HCW from 8 cohorts being vaccinated with at least 1 dose and with available information on immunization status at 6 months.
The analyses showed that women had higher serological response at 6 months, while ageing was inversely related to it. We observed a reduction in the serological response at 6 months, as well as a negative trend in antibody levels when considering serial serologies, demonstrating their progressive waning. With regard to past COVID-19 infection, our study showed that HCWs with COVID-19 infection prior to vaccination were more likely to maintain positive response at 6-months, also corresponding to higher immunogenicity levels. Our analysis also showed that mRNA vaccines confer higher protection than viral vector vaccine.

Recommendations

This study represents an important source of information to understand the effectiveness and the duration of immune response acquired by vaccination. We provided novel information on the ability of different types of vaccines to elicit immunogenicity, and time-trends of their immunological effect over six months. This analysis adds useful information to help in the prioritization of candidates for vaccination campaign.

We plan to extend the follow-up of this ORCHESTRA cohort of HCW and to expand it to investigate the lifestyle and sociodemographic determinants of immune response and duration, as well as proceeding the analysis on temporal trends of serological levels.

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References

1- Singu S, Acharya A, Challagundla K, Byrareddy SN. Impact of Social Determinants of Health on the Emerging COVID-19 Pandemic in the United States. Front Public Health. 2020 Jul 21;8:406.

2- Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford- AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021 May 13;373:n1088.

3- Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov. 2018 Apr;17(4):261-279.

4- Fiolet T, Kherabi Y, MacDonald CJ, Ghosn J, Peiffer-Smadja N. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. Clin Microbiol Infect. 2022 Feb;28(2):202-221.

5- Joint Committee on Vaccination and Immunisation. Advice on priority groups for COVID-19 vaccination, 30 December 2020. London, Department of Health and Social Care, 2020. Available at https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19- vaccination-advice-from-the-jcvi-30-december-2020/joint-committee-on-vaccination-and- immunisation-advice-on-priority-groups-for-covid-19-vaccination-30-december-2020

6- Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021 Apr 15;384(15):1412-1423.

7- Vallée A, Vasse M, Mazaux L, et al.An Immunogenicity Report for the Comparison between Heterologous and Homologous Prime-Boost Schedules with ChAdOx1-S and BNT162b2 Vaccines. J Clin Med. 2021 Aug 25;10(17):3817.

8- Zimmermann P, Curtis N. Factors That Influence the Immune Response to Vaccination. Clin Microbiol Rev. 2019 Mar 13;32(2):e00084-18.

9- Cho A, Wrammert J. Implications of broadly neutralizing antibodies in the development of a universal influenza vaccine. Curr Opin Virol. 2016 Apr;17:110-115.

10- Collier AY, Yu J, McMahan K, et al. Differential Kinetics of Immune Responses Elicited by Covid-19 Vaccines. N Engl J Med. 2021 Nov 18;385(21):2010-2012.

ORCHESTRA has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101016167

11- Mehul S. Suthar, Prabhu S, et al. Durability of immune responses to the BNT162b2 mRNA vaccine. bioRxiv2021.09.30.462488.

12- Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet. 2021 Oct 16;398(10309):1407-1416.

13- Zhong D, Xiao S, Debes AK, et al. Durability of Antibody Levels After Vaccination With mRNA SARS-CoV-2 Vaccine in Individuals With or Without Prior Infection. *JAMA.* 2021;326(24):2524–2526.

14- Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta- regression. Lancet. 2022 Mar 5;399(10328):924-944.

15- https://orchestra-cohort.eu

16- DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–87.

17- Jiggins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis, Stat. Med. 2002;21:1539–1558.

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