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Vaccination status among COVID-19 patients and duration of Polymerase Chain Reaction test positivity: evaluation of immunization schedule and type of vaccine

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Keywords: COVID-19; vaccine; booster; molecular buffer; PCR positivity
Parole chiave: COVID-19; vaccino; booster; buffer molecolare; positività alla PCR

Abstract

Background. *The introduction of the vaccine against SARS-CoV-2 has represented a cornerstone in the containment of the pandemic. Our aim was to assess the vaccination schedules in relation to the infection free interval and to the duration of positivity in case of infection.*
Study design. *This study involves the SARS-CoV-2 infected people managed by the Local Health Authority ASL 1 Abruzzo. The data collected included: vaccine administration date, vaccine type, information on the Polymerase Chain Reaction test positivity, and demographic variables, such as age and sex.*
Methods. *The duration of Polymerase Chain Reaction test positivity was assessed in relation to the vaccination status, the vaccine type and the time interval between the last vaccination dose and the first nasopharyngeal positive swab over the considered period.*
Results. *The infection duration (DAYS) was significantly shorter in subjects vaccinated with a booster dose than unvaccinated subjects (12.8 vs 14.6; p<0.0001) and subjects vaccinated with the primary series only (12.8 vs 14.1; p<0.0001). Duration of PCR positivity was shorter with heterologous immunisation than with other vaccination schedules (p=0.0317).*
Conclusions. *This study highlights, in a large cohort of patients, the association between vaccination schedule and the response to infection.*

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Introduction

The coronavirus disease-19 (COVID-19) is represented by the "severe acute respiratory syndrome Coronavirus 2" (SARS-CoV-2), the second coronavirus responsible for severe acute respiratory syndrome (SARS): the first SARS-CoV virus emerged in 2002 (1).

As 2019 turned into 2020, a coronavirus spilled over from wild animals into people, sparking what has become a pandemic that deeply influenced, and is still influencing, our society by profoundly modifying the usual behaviors (2) and deeply affecting people psychophysical health (3). On December 31, 2019, the outbreak of cases was officially reported to the World Health Organization (WHO) by the Chinese authorities. The virus isolation has allowed to develop reliable diagnostic tools and effective vaccines (4). The incubation period for SARS-CoV-2 is usually 4 or 5 days. However, a follow up survey has shown that a significant proportion of COVID-19 recovered subjects report one or more persistent symptoms, even weeks or months following acute illness (i.e., the "long COVID syndrome") (5).

The main and most reliable diagnostic tool is the nasopharyngeal (NP) swab which detects and amplifies the genome of the SARS-CoV-2 virus in the biological sample using the RT/PCR (*Reverse Real Time/polymerase chain reaction*) method (6).

Molecular positivity swab testing proved to be critical for the containment of the COVID-19 pandemic. Molecular diagnostic tests, such as the PCR test, are highly sensitive and specific in detecting the viral RNA and they are recommended by the WHO to confirm the diagnosis of symptomatic subjects and to implement public health measures (7).

From the outbreak of the pandemic to 10 January 2024, more than 26 million cases were diagnosed in Italy. A flash survey of December 2023 conducted by the Italian National Health Institute on the prevalence and distribution of the SARS-CoV-2 variants of concern for public health in Italy, reported that the JN.1 variant is the only variant showing a sustained circulation in Italy. From 08 January 2024 to 14 January 2024, 42.0% of the total documented cases were reinfections (8). Epidemic management required great efforts from the institutions, and it required a profound Health System reorganization (9).

With regard to the geographical area covered by the Local Health Authority ASL1 Abruzzo (an Italian public body which is part of the regional or provincial healthcare authority) 60,715 cases were recorded on the Open Data Covid surveillance system from the pandemic outbreak to 13 February 2023 (10). In the same area, from 11 December 2023 to 17 December 2023, a new rapid escalation of COVID-19 infections was recorded (11).

The introduction of the vaccine against SARS-CoV-2 in Italy, provided free of charge to everyone, has represented a cornerstone in the containment of the pandemic. Indeed, vaccines have reduced incidence of the infections, severity of the infections and their sequelae, and the hospital admission rates and deaths (12).

In Italy, the vaccination campaign began on 27 December 2020, under the provisions of the Vaccines National Strategic Plan for the prevention of SARS-CoV-2 infections, which had identified some priority groups to receive vaccination. To date, the European Medicines Agency (EMA) and the Italian Medicines Agency (AIFA) have authorised five vaccinations: Comirnaty (Pfizer/BioNtech), COVID-19 Vaccine Moderna (Moderna), Vaxzevria (AstraZeneca), Nuvaxovid (Novavax) and COVID-19 Vaccine Janssen (Johnson&Johnson). The first four vaccines are administered in a 2 dose schedule; the Janssen vaccine is scheduled in a single dose (13, 14).

By September 24, 2023, 145,134,032 doses of which 40,494,455 third doses had been administered in Italy to people 12 years and over (49,524,332 first doses, 48,730,287 second/single doses). On 16 December 2021, the national health system vaccination programme began to roll out to 5–11 year old children. On September 24, 2023, first dose of COVID-19 vaccine was administered to 38.6% of this age group, and second dose coverage reached 35.4% (15). During the Omicron variant surge (from 3 January 2022), vaccine effectiveness, i.e., risk reduction for vaccinated subjects compared to unvaccinated subjects, was 40% within 90 days after completion of the vaccination series, 31% at 91-120 days, and 44% at >120 days after completion of the vaccine series; vaccine effectiveness was at 57% after the additional/booster dose. Evidence indicates that vaccine effectiveness against severe disease was 71% for vaccinated subjects who had completed the vaccine series after less than 90 days, 70% at 91-120 days after completion of the vaccine series, and 72% at >120 days after completion of the vaccine series; vaccine effectiveness was at 88% after the additional/booster dose (16).

By February 13, 2023, 250,734 subjects, i.e., 86.5% of the overall patients referring to the Local Health Authority ASL1 Avezzano-Sulmona-L'Aquila,

had completed the primary vaccine series (2 doses or 1 dose for single dose vaccine), and 183,915 subjects had received the third dose (10).

Aim of this study was to assess the vaccination schedules in relation to the infection-free interval and to the duration of positivity in case of infection. The duration of the NP swab PCR positivity was assessed in relation to the vaccination status (unvaccinated, vaccinated with primary vaccine series, vaccinated with booster dose), to the vaccine type (Pfizer, Moderna, AstraZeneca, Janssen), and to the time interval between the last vaccination dose and the first NP positive swab over the period considered, among the patients referring to the Local Health Authority ASL1 Avezzano-Sulmona-L'Aquila.

Methods

We enrolled all those individuals who had tested positive for SARS-CoV-2 by NP swab from 1 November 2021 to 31 January 2022 ('fourth wave'), across the territory covered by Local Health Authority ASL1 Avezzano-Sulmona-L'Aquila. Molecular swabs were analyzed by the Aptima™ SARS-CoV-2 assay, a nucleic acid amplification in vitro diagnostic test intended for the qualitative detection of RNA from SARS-CoV-2 isolated and purified from nasopharyngeal, available in different laboratories. The data collected included: vaccine administration date (first, second and third dose), vaccine type, information on the NP swab PCR positivity (dates of positive and negative test results), and demographic variables, such as age and sex.

The study was approved by the Ethical Committee of the Local Health Authority for the Provinces of L'Aquila and Teramo (report n° 13 dated 23 March 2022).

Continuous variables are presented as mean ± standard deviation (SD), and median (min/max); while categorical variables are presented as percentages. Kolmogorov–Smirnov test was used to evaluate the normality of distribution of continuous variables, and according to its results, the Student's t-test or Mann–Whitney test were used for variable comparison. To compare three or more groups, Kruskal-Wallis test was used, and Dunn's Test was used to perform pairwise comparisons. Spearman's rank correlation was used to assess the relationship between continuous variables. A p-value < 0.05 was considered statistically significant when comparing variables. All the statistical analyses were performed using STATA 14.0 software.

Results

Overall, 5,022 COVID-19 cases were identified by NP swab PCR: 2,585 Females (51.5%) and 2,437 Males (48.5%). The sample mean age was 35.8 (±22.0). Among them, 2,058 subjects (41.0%) did not receive vaccination; 2,889 subjects (57.5%) completed the primary vaccine series with two doses; 20 subjects (0.4%) received the additional dose (recommended for immunocompromised subjects), and 55 subjects (1.1%) received a single dose.

Among the vaccinated subjects with primary series: 2,045 received Pfizer, 402 Moderna, 409 AstraZeneca, 1 Janssen, and 91 received heterologous vaccination (AstraZeneca/Moderna; AstraZeneca/Pfizer). None of the study subjects received the Novavax vaccine. Only 748 subjects (14.9%) received the booster dose (360 Pfizer, 388 Moderna). The time interval from the last vaccine dose and the positivity diagnosis was 115.0 days (±65.9) and the duration of the NP swab PCR positivity was 14.1 days (±7.6).

We did not register any significant difference in the time interval (measured in days) between the last dose received and PCR positivity, and in the duration of PCR positivity between males and females.

Vaccinated individuals showed a significant reduction of PCR positivity duration versus unvaccinated individuals (13.8 days vs 14.6 days; p = 0.0002). The subjects who received the booster dose showed a shorter duration of PCR positivity (12.8 vs 14.1; p <0.0001) (Fig. 1).

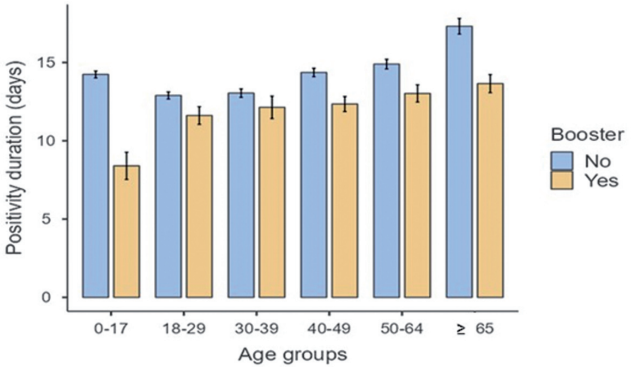

Fig. 1 - Mean duration of PCR positivity, measured in days, by age group and booster dose.

Tab. 1 - Average, standard deviation, median, minimum, maximum value of the duration of positivity for each age group, and p-value between groups.

Age	Average	SD	Median	Min	Max	p-value*
0-17 years	14.2	8.1	12	1	86	0.0001
18-29 years	12.7	6.1	11	1	51	
30-39 years	12.9	6.5	11	1	53	
40-49 years	14.0	6.7	13	1	51	
50-64 years	14.5	7.8	13	1	67	
≥ 65 years	16.2	8.7	15	1	60	

SD= standard deviation
* Kruskal-Wallis test

Tab. 2 - Average, standard deviation, median, minimum, and maximum value of the time intervals measured in days between vaccination and positive test by type of primary vaccine.

Primary vaccine	Average	SD	Median	Min	Max	p-value*
Pfizer	111.3	65.4	119	0	317	0.0001
Moderna	117.2	59.8	129	1	280	
AstraZeneca	129.1	71.5	143	0	261	
Heterologous	121.4	66.2	141	3	212	

SD= standard deviation; *Kruskal-Wallis test

Tab. 3 – Average, standard deviation, median, minimum and maximum values of the of PCR positivity Pfizer vaccination is associated with a significantly shorter disease-free period versus AstraZeneca and heterologous vaccination. Moderna shows a statistically significant reduced disease-free period versus AstraZeneca. AstraZeneca is also associated to a longer duration of positivity versus the other vaccines (Tab. 4). The Janssen vaccine was only administered once.

Vaccine	Average	SD	Median	Min	Max	p-value*
Pfizer	13.7	7.3	12	0	67	0.0317
Moderna	13.6	7.4	12	1	52	
AstraZeneca	14.5	7.1	14	1	59	
Janssen	29	.	29	29	29	
Heterologous	13.0	6.3	11	1	29	

*Kruskal-Wallis test

Tab. 4 – Primary vaccine and disease-free period and primary vaccine and positivity duration pairwise comparison through Dunn test

	Pfizer	Moderna	Astra Zeneca	Janssen
Primary vaccine and disease-free period				
Moderna	0.0932			
AstraZeneca	<0.0001	0.0020		
Janssen	0.2724	0.2971	0.3710	
Heterologous	0.0362	0.1507	0.2347	0.3405
Primary vaccine and positivity duration				
Moderna	0.3717			
AstraZeneca	0.0051	0.0128		
Janssen	0.0498	0.0482	0.066	
Heterologous	0.2435	0.3129	0.0328	0.0434

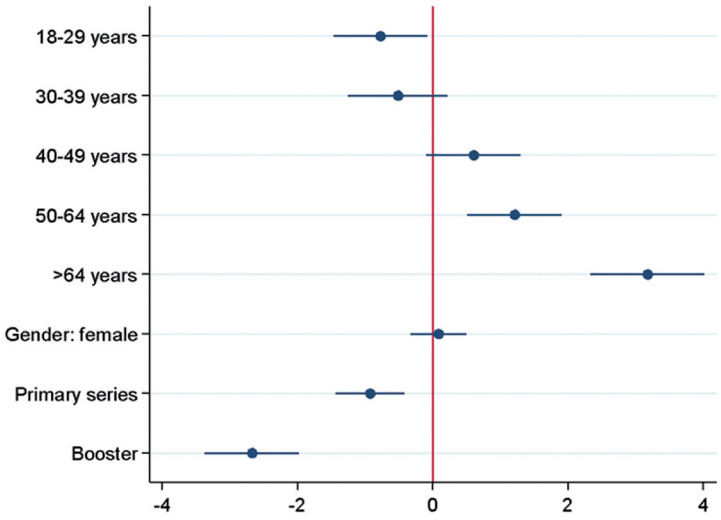

Fig. 2 - Correlation coefficients of the multiple linear regression with 95% CI of the duration of positivity with the listed variables. The vertical red line represents the absence of association. Negative values indicate a negative association with the duration of positivity with the listed variables.

Table 1 shows that the duration of positivity measured in days globally increased with age, except for the youngest (0-17 years) (Tab. 1).

We analysed the association between the disease-free period (time without COVID positivity in days) and the four different primary vaccinations. Table 2 illustrates the comparisons of the time intervals measured in days between the last dose received and the PCR positivity. The highest average interval is associated with the Astra Zeneca vaccination (129.1 days) (Tab. 2). We also analysed any differences in the duration of PCR positivity in relation to the received primary vaccine type. Pfizer and Moderna showed a shorter positivity duration versus AstraZeneca. Heterologous vaccination showed the shortest positivity duration (Tab. 3).

Finally, the linear regression model (Fig. 2, Tab. 5) shows that age and anti-COVID vaccination had a significant impact on the duration of PCR positivity. Adults aged > 50 years and, to a greater extent, ≥65 years, had a longer PCR positivity. Completion of vaccination series and being in the 18-29 age group seemed to reduce the duration of positivity. Evidence shows that the booster dose further reduced the

Tab. 5 - Multiple linear regression with 95% CI of the duration of positivity with the listed variables

Variable	Coefficient	Confidence Interval 95%		p-value
Age				
0-17 years	Rif.			
18-29 years	-0.78	-1.47	-0.08	0.028
30-39 years	-0.52	-1.25	0.22	0.172
40-49 years	0.61	-0.09	1.30	0.091
50-64 years	1.21	0.51	1.91	0.001
≥ 65 years	3.17	2.33	4.01	<0.0001
Gender				
Male	Rif.			
Female	0.09	-0.33	0.50	0.685
Vaccine status				
Unvaccinated	Rif.			
Primary cycle	-0.93	-1.43	0.42	<0.0001
Booster	2.67	-3.37	-1.97	<0.0001

duration of PCR positivity. Sex-related differences had no impact on the duration of positivity.

Discussion

On 24 November 2021, the World Health Organization reported a new SARS-CoV-2 variant, B.1.1.529, named 'Omicron' (17).

Preliminary evidence suggests that the Omicron variant has a higher transmission rate and vaccine resistance (18).

Studies have demonstrated that vaccine effectiveness against hospitalization and death from severe COVID-19 disease wanes after two dose COVID-19 vaccines. In addition, some studies have concluded that booster dose vaccination with any of the mRNA-based vaccines significantly reduces reinfection risk and, even if infected, disease may be mild. (19).

A study conducted by Nemet et al. has reported a higher neutraliztion efficiency against the Omicron variant among the healthcare workers who had received three vaccine doses versus the health care workers who had received two vaccine doses. However, even with three vaccine doses, Omicron variant showed lower neutralizing sensitivity than the Delta variant (19, 20).

A recent American study examined the association between the administration of three doses of Pfizer/BioNTech or Moderna vaccine and symptomatic SARS-CoV-2 infection caused by the Omicron and Delta variants. The study has demonstrated that subjects who had received three doses of mRNA COVID-19 vaccine (vs. unvaccinated subjects and vs. two doses) were less likely to develop symptomatic SARS-CoV-2 infection compared with controls (21). A study conducted on patients who had received a RT/PCR test for SARS-CoV-2 after two doses of mRNA BNT162b2 vaccine, reported a significant increase in the risk of infection among patients who had received their second vaccine dose at least 146 days before the RT/PCR test, particularly among patients older than 60 years (22).

A retrospective case control study conducted in Israel has demonstrated an association between receipt of the booster dose and reduction in the odds of testing positive for SARS-CoV-2 within two weeks of receipt of the booster versus two dose vaccine (23). However, another study has demonstrated that, although antibody titres increased with the fourth BNT162b2 booster dose, the antibody titres against Omicron infections are still insufficient (24).

A study published in January 2022 reported that the odds of post vaccination infection were significantly lower in vaccinated than unvaccinated individuals. Additionally, the time interval of the infection onset varied from few days post vaccination to >4 months after completion of the vaccination schedule (min 5 days, max 139 days, median 55 days post vaccination). The duration of PCR positivity among the vaccinated subjects was significantly shorter than post natural infections occurred after natural infections. Breakthrough infections are rare and significantly less frequent compared with reinfection after natural infection, in particular among the responders. In addition, the duration of positivity among vaccinated individuals is significantly shorter than the duration of reinfection after natural infection, suggesting that post vaccination viral shedding is likely very limited (25).

In alignment with the literature review, our observational study claims that the receipt of the anti COVID vaccination and of the booster dose reduces the duration of NP swab PCR positivity in a large sample of subjects referring to the Local Health Authority ASL1 Abruzzo.

The infection duration is significantly shorter in subjects vaccinated with a booster dose than unvaccinated subjects and subjects vaccinated with the primary series only. Duration of PCR positivity was shorter with heterologous immunisation than with other vaccination schedules.

Vaccination effectiveness against duration of PCR positivity appears to decline among subjects aged >50 years and, to a greater extent, among subjects aged ≥65 years. On the other hand, the duration of positivity decreased for subjects in the 18-29 age group.

The longer duration of PCR positivity in the 0-17 age group may be explained by the poor adherence to the immunisation schedules as some categories cannot get vaccinated against COVID-19. The difference related to the age variable is possibly due to a reduced adaptive immune response in older individuals (26), i.e., immunosenescence. Older individuals are known to have reduced vaccine responses, especially due to a decreased humoral and cellular immune response (27-29).

The analysis performed to assess the relationship between the duration of positivity and type of vaccine received, highlights that heterologous vaccination is associated with a shorter duration of PCR positivity.

The time interval elapsed between the receipt of the last dose and the date of positive test seems to be longer among those who received AstraZeneca or heterologous vaccination. On the other hand, Pfizer

and Moderna show a relatively shorter time interval between the receipt of the last vaccine dose and infection.

Although our study encourages and supports vaccinations, it also has some limitations. The main limitation is the lack of knowledge of previous SARS-CoV-2 infection (with respect to the study start date), which might have affected the disease free interval and the duration of PCR positivity over the period considered. Other possible limitations of our study were the unperformed variant typing, the use of molecular testing only (versus antigen testing), the lack of other demographic variables and of variables related to the health status of the subjects enrolled (e.g., subjects with comorbidities or with weakened immune system).

Conclusions

This study supports and encourages the large scale use of vaccination. However, there is a paucity of conclusive data on the impact of some variables that might affect the duration of positivity and the time interval between the last vaccine dose received and a COVID-19 infection episode. An in depth study of these data would identify specific groups with different immune responses to vaccine. This aspect is critical to plan risk stratification methods in the national healthcare service.

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Riassunto

Status vaccinale in pazienti affetti da COVID-19 e durata della positività al test della reazione a catena della polimerasi: valutazione dell'immunizzazione e del tipo di vaccino

Introduzione. L'avvio delle vaccinazioni contro il SARS-CoV-2 ha rappresentato un punto di svolta nel contenimento della pandemia. Lo scopo del presente studio è valutare l'intervallo di tempo corrispondente all'assenza di malattia in relazione allo stato vaccinale e alla durata della positività in caso di infezione.

Disegno dello studio. Lo studio include pazienti infettati da SARS-CoV-2 afferenti alla Azienda sanitaria locale 1 Abruzzo. I dati raccolti includono: data di somministrazione del vaccino, tipo di vaccino, informazioni sulla durata di positività e variabili demografiche come età e sesso.

Metodi. La durata della positività mediante test della reazione a catena della polimerasi è stata valutata in relazione allo stato vaccinale, al tipo di vaccino, all'intervallo di tempo intercorso tra l'ultima dose vaccinale e il primo tampone nasofaringeo risultato positivo nel periodo considerato.

Risultati. La durata dell'infezione (IN GIORNI) è risultata significativamente più breve in soggetti vaccinati con dose booster rispetto a soggetti non vaccinati (12.8 vs 14.6; $p<0.0001$) e a soggetti che hanno subìto soltanto le prime dosi vaccinali (12.8 vs 14.1; $p<0.0001$). La durata della positività è risultata inferiore nei soggetti sottoposti a vaccinazione eterologa rispetto ad altri tipi di vaccinazione ($p=0.0317$).

Conclusioni. Lo studio evidenzia l'associazione tra la vaccinazione e la risposta all'infezione in un ampio campione di pazienti.

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