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**To cite this article:** Domenico Pascucci, Alberto Lontano, Luca Regazzi, Eleonora Marziali, Mario Cesare Nurchis, Matteo Raponi, Giuseppe Vetrugno, Umberto Moscato, Chiara Cadeddu & Patrizia Laurenti (2023) Co-administration of SARS-CoV-2 and influenza vaccines in healthcare workers: Results of two vaccination campaigns in a large teaching hospital in Rome, *Human Vaccines & Immunotherapeutics*, 19:3, 2287282, DOI: [10.1080/21645515.2023.2287282](https://doi.org/10.1080/21645515.2023.2287282)

**To link to this article:** <https://doi.org/10.1080/21645515.2023.2287282>



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Published online: 28 Nov 2023.



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RESEARCH ARTICLE



## Co-administration of SARS-CoV-2 and influenza vaccines in healthcare workers: Results of two vaccination campaigns in a large teaching hospital in Rome

Domenico Pascucci<sup>a,b,\*</sup>, Alberto Lontano<sup>b,\*</sup>, Luca Regazzi<sup>b</sup>, Eleonora Marziali<sup>b</sup>, Mario Cesare Nurchis<sup>b,c</sup>, Matteo Raponi<sup>d</sup>, Giuseppe Vetrugno<sup>a,e</sup>, Umberto Moscato<sup>b,d</sup>, Chiara Cadeddu<sup>b</sup>, and Patrizia Laurenti<sup>b,d</sup>

<sup>a</sup>Health Management, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; <sup>b</sup>Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, Rome, Italy; <sup>c</sup>School of Economics, Università Cattolica del Sacro Cuore, Rome, Italy; <sup>d</sup>Department of Women, Child and Public Health Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; <sup>e</sup>Department of Health Surveillance and Bioethics, Università Cattolica del Sacro Cuore, Rome, Italy

### ABSTRACT

The concurrent administration of COVID-19 and influenza vaccines has arisen as a promising approach to bolster protection against respiratory pathogens and improve vaccination rates. However, there remains a lack of data regarding the prevalence of co-administration across several vaccination campaigns, especially among healthcare workers (HCWs). Therefore, this study aims to shed light on the acceptance of co-administration strategies among HCWs during the two campaigns following the introduction of the anti-SARS-CoV-2 vaccine. A retrospective cohort study was conducted among the HCWs of the Fondazione Policlinico Universitario “A. Gemelli” IRCCS, a research hospital in Rome. Hospital administrative databases were accessed to gather information about vaccination for SARS-CoV-2 and influenza during the 2021/2022 and 2022/2023 vaccination campaigns. The study included 7399 HCWs. The co-administration of anti-SARS-CoV-2 and influenza vaccines presented a significant rise in 2022/2023 compared to the previous vaccination campaign (+38%): this was confirmed for every professional category, with the largest increases among resident doctors (+47%) and physicians (+44%), and also for every age category, but it was particularly evident for the youngest health professionals. The probability of co-administration uptake during the 2022/2023 campaign was significantly higher for males, and for those that received co-administration during the 2021/2022 campaign, while the probability was lower for nurses and administrative staff. This study highlights the co-administration procedure as a valuable and effective tool in annual vaccination campaigns for SARS-CoV-2 and influenza. The procedure’s safety and streamlined logistics make it increasingly attractive for implementation, particularly among HCWs.

### ARTICLE HISTORY

Received 12 August 2023  
Revised 7 November 2023  
Accepted 20 November 2023

### KEYWORDS

Co-administration; vaccine; SARS-CoV-2; COVID-19; influenza; healthcare workers

### Introduction

The ongoing global health crisis caused by the COVID-19 pandemic, coupled with the seasonal burden of influenza, has prompted the urgent need for innovative strategies to safeguard public health.<sup>1</sup> Vaccination remains a crucial tool in controlling infectious diseases, and the coadministration of COVID-19 and influenza vaccines has emerged as a potential approach to enhance protection against respiratory pathogens, reduce strain on healthcare services, and streamline vaccination efforts.<sup>2</sup>

For healthcare workers (HCWs), the implementation of coadministration offers several advantages. By consolidating vaccinations, it reduces the number of healthcare visits required and provides timely protection against both diseases, which could lead to increased vaccine uptake among HCWs and the general population. Additionally, from a healthcare system organization and management perspective, this approach could bolster resilience during public health emergencies by alleviating the burden on healthcare services.<sup>3,4</sup>

Recent evidence indicates that co-administering COVID-19 vaccines with inactivated vaccines, such as seasonal influenza

vaccines (SIVs), is well-tolerated in terms of immunogenicity and reactogenicity.<sup>2,5</sup> Notably, a recent randomized phase IV placebo-controlled study has substantiated the safety of concurrently administering ChAdOx1 and BNT162b2 COVID-19 vaccines with MF59-adjuvanted or cell culture-derived SIVs, without any clinically significant escalation in adverse events or immunological interference.<sup>6</sup> Similarly, a substudy nested within a phase III trial has demonstrated the safety, immunogenicity, and efficacy profile of the NVX-CoV2373 COVID-19 vaccine when co-administered with SIVs, albeit with higher occurrences of reactogenicity events in the co-administration group.<sup>7</sup>

Overall, the available studies appear to support the non-inferiority of coadministration compared to individual administration for COVID-19 and influenza vaccines.<sup>2</sup> Nevertheless, certain investigations have reported a higher prevalence of mild adverse effects related to reactogenicity in patients who underwent coadministration,<sup>7,8</sup> which may, in part, contribute to increased vaccine hesitancy for co-administered vaccines when compared to single vaccines.<sup>8,9</sup>

**CONTACT** Domenico Pascucci ✉ [domenico.pascucci@outlook.it](mailto:domenico.pascucci@outlook.it) 📍 Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo A. Gemelli 8, Rome 00168, Italy.

\*These authors contributed equally to this work.

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Given the importance of coadministration in enhancing vaccine coverage, public health authorities, including the World Health Organization (WHO),<sup>5</sup> the US Centers for Disease Control and Prevention (CDC),<sup>10</sup> the US Advisory Committee on Immunization Practices (ACIP),<sup>11</sup> and the Italian Ministry of Health,<sup>12</sup> endorse the simultaneous administration of COVID-19 vaccines with other vaccines, including seasonal influenza.

However, despite support from public health authorities, patient acceptance of coadministration campaigns, even among HCWs, remains a critical concern. A survey conducted among the general population in Italy<sup>13</sup> identified that among 2463 participants, 22.9% expressed a favorable attitude toward vaccine co-administration, whereas 16.6% firmly declined to receive both vaccines simultaneously. The remaining 60.5% exhibited varying degrees of hesitancy. The main determinants influencing positive attitudes toward vaccine co-administration were found to be compliance with the primary COVID-19 vaccination schedule, and trust in public health institutions. Furthermore, a survey conducted among a sample of 2381 Italian HCWs<sup>14</sup> revealed that 51.0% of HCWs expressed hesitancy toward coadministration, while residents and nurses exhibited the highest propensity to receive it.

Data on the trend of co-administration of anti-SARS-CoV-2 and influenza vaccines across several vaccination campaigns, particularly among HCWs, is still lacking.

This study aims to address this knowledge gap and provide insights into the acceptance of co-administration strategies for HCWs in the two campaigns following the introduction of anti-SARS-CoV-2 vaccine.

## Materials and methods

### Study design

A retrospective cohort study was conducted to evaluate the anti-SARS-CoV-2 and the influenza vaccination coverage and to assess the acceptance of the co-administration of these two vaccines among the HCWs of the Fondazione Policlinico Universitario “A. Gemelli” IRCCS, an Italian high complexity research hospital based in Rome. All personnel were offered vaccination by the hygiene unit of the hospital, from October 6<sup>th</sup> 2022 to December 22<sup>nd</sup> 2022.

### Inclusion criteria

The personnel working at hospital units of Fondazione Policlinico Universitario “A. Gemelli” IRCCS, who gave written informed consent, were included.

### Ethical board approval

The study protocol was approved by the Ethical Board of Fondazione Policlinico Universitario “A. Gemelli” IRCCS with the approval number 0031526/22 ID 5169.

## Organization of the COVID-19 and influenza vaccination campaign

The Local Health Unit offered the vaccines free of charge to the HCWs in accordance with the Italian “Piano Nazionale Prevenzione Vaccinale.”<sup>15</sup>

The vaccination campaign was run by specialist medical doctors in hygiene and preventive medicine, occupational medicine, resident medical doctors from the same units, and nurses.

Hospital personnel were required to book their vaccinations through a dedicated information system on the intranet of the healthcare facility. They could choose between receiving the anti-SARS-CoV-2 vaccine, the influenza vaccine, or both. Additionally, they were asked to select a specific time slot for the vaccination session on designated days identified by the organizers of the vaccination campaign.

For this purpose, five groups of two days each were identified, spaced approximately three weeks apart during the period from October to December 2022.

It was possible for individuals to receive the influenza vaccination on a different day from the anti-SARS-CoV-2 vaccination. Nonetheless, the co-administration of both vaccines was encouraged as a method to increase compliance among HCWs.

Moreover, HCWs who showed up without a prior appointment were also vaccinated.

The vaccine offered for anti-SARS-CoV-2 immunization comprises the Comirnaty Original/Omicron BA.4–5 bivalent mRNA vaccine (Pfizer/BioNTech)<sup>16</sup> for SARS-CoV-2 as a booster dose. The active components of the COVID-19 mRNA Vaccine are tozinameran and famtozinameran. Each multidose vial contains 6 doses of 0.3 mL. It can be administered intramuscularly as a single 0.3 mL dose for individuals. The recommended injection site is the deltoid muscle in the upper arm and should be given at least 3 to 6 months after completing the primary vaccination series and/or receiving a previous booster dose of any SARS-CoV-2 vaccine. On the other hand, there were three available influenza vaccines, and the selection was made by the physician based on the risk conditions of HCWs:

- Vaxigrip Tetra by Sanofi Pasteur:<sup>17</sup> a quadrivalent inactivated split influenza virus vaccine containing antigens, designed to prevent influenza disease caused by the two subtypes of influenza A virus and the two types of influenza B virus present in the vaccine. The vaccine strains are cultivated in fertilized hen eggs. It is administered via intramuscular or subcutaneous injection, with the preferred site for intramuscular injection being the deltoid muscle of the upper arm. Each pre-filled syringe contains 0.5 mL of the vaccine, and it is recommended for use in HCWs under the age of 65.
- Flud Tetra by Seqirus:<sup>18</sup> a quadrivalent inactivated surface antigen vaccine, adjuvanted, containing proteins from four distinct inactivated influenza A and B virus strains cultivated in fertilized hen eggs. It is administered exclusively through intramuscular injection, preferably in the deltoid muscle. Each pre-filled syringe contains 0.5 mL of the vaccine, and it is

recommended for use in HCWs who are over 65 years of age or those with compromised immune systems.

- Flucelvax Tetra by Seqirus:<sup>19</sup> a quadrivalent inactivated surface antigen vaccine prepared in cell cultures. It includes both A and B strains of the influenza virus. It is administered via intramuscular injection in the deltoid muscle, with each prefilled syringe containing 0.5 mL of the vaccine. Its use is recommended for HCWs who are allergic to egg proteins.

### Data sources

Hospital administrative databases were accessed to gather information about vaccination during the 2021/2022 and 2022/2023 vaccination campaigns at Fondazione Policlinico Universitario “A. Gemelli” IRCCS.

A separate database was created, assigning a distinctive anonymous identifier to each person along with their respective professional occupation details. Socio-demographic data, such as age and gender, were obtained using the individual employee tax code, while occupation-related data were acquired from the hospital’s human resources unit.

### Statistical analysis

In order to ensure the comparability of the vaccination coverage data and to assess its trend over time, the two databases for the years 2021/2022 and 2022/2023 were compared, keeping only the health workers contained in both.

Age classes were created using age quartiles as limit values.

McNemar’s test was used to make comparisons of vaccine coverage for SARS-CoV-2, influenza vaccine and co-administration of the two vaccines for the years 2021/2022 and 2022/2023: these comparisons were then also stratified by occupational category and, for co-administration only, by age group.

In addition, a multivariable logistic regression model was designed to assess the influence of gender, age, occupational category, and co-administration in the year 2021/2022 on co-administration in the 2022/2023 vaccination campaign.

Based on the assumption of the model, the dependent variable was dichotomized into HCWs who received co-administration in 2022/2023 and those who did not. The Hosmer – Lemeshow (HL) goodness of fit test was run to test how well the data fit the logistic model. A significance higher than 0.05 showed a good model fitness.<sup>2</sup>

The significance level of the statistical analyses was set at 5%.

The analyses were run on STATA 17 (StataCorp LP, College Station, TX, USA).

### Results

In 2021/2022 and 2022/2023 vaccination campaigns 7399 HCWs were observed. 60.51% of them were women, and the median age was 41. The most represented professional category was nurses (29%), followed by resident doctors (20.08%), physicians (19.35%), other HCWs (16.80%) and administrative staff (14.75%). Table 1 depicts sociodemographic characteristics of the sample analyzed.

**Table 1.** Sociodemographic characteristics of the sample analyzed.

Variable	N	N (%)
<b>Age class</b>		
23–31	2,074	28.03
32–41	1,654	22.35
42–52	1,853	25.04
53–84	1,818	24.57
<b>Sex</b>		
F	4,477	60.51
M	2,922	39.49
<b>Professional category</b>		
Physicians	1,432	19.35
Resident doctors	1,486	20.08
Nurses	2,147	29.02
Other HCWs **	1,243	16.80
Administrative staff	1,091	14.75
Tot	7,399	100.00

\*\*The category “Other HCWs” includes midwives, healthcare assistants, pharmacists, psychologists, laboratory technicians, radiology technicians, physiotherapists, speech therapists, perfusionists, neurophysiopathology technicians, biologists, environmental and occupational prevention technicians, dieticians, orthoptists, audiometrists, occupational therapists and neuro- and psychomotricity therapists for children and adolescents.

The number of HCWs that received anti-SARS-CoV-2 and influenza vaccination decreased significantly between 2021/2022 and 2022/2023 campaign both considered in total or stratified by professional category. Concerning the anti-SARS-CoV-2 vaccine total uptake, the most important reduction was recorded in the category “other HCWs” (–78 p.p.) and among nurses (almost –72 p.p.), while the smallest reduction was reported among resident doctors (–43 p.p.).

As for the influenza vaccine, the reduction was less striking, and the lowest-performing category were “other HCWs” (–10 p.p.) and resident doctors (–10 p.p.), while the smallest reduction was recorded among administrative staff (–2 p.p.) (Table 2).

The co-administration of anti-SARS-CoV-2 and influenza vaccines presented a significant rise in 2022/2023 compared to the previous vaccination campaign: this was confirmed for every professional category, with the largest increases among resident doctors (+47 p.p.) and physicians (+44 p.p.) (Table 2), and for every age category, but was particularly evident for the youngest health professionals (Table 3).

The multivariable logistic regression model (Table 4) showed no association between anti-SARS-CoV-2 and influenza vaccines co-administration acceptance and age category.

Interestingly, the male gender presented a weak to modest association with co-administration uptake (OR 1.53 95% CI [1.23; 1.90]).

As for professional category, the category “other HCWs” showed a moderate negative association with co-administration acceptance (OR 0.37 95% CI [0.26; 0.53]), while nurses and administrative staff had a modest negative association with co-administration acceptance (OR 0.49 95% CI [0.37; 0.67] and OR 0.65 95% CI [0.48; 0.87], respectively).

Finally, having received co-administration of vaccines in 2021/2022 had a modest association with the attitude of receiving both vaccines in the same vaccination session during the 2022/2023 campaign (OR 1.63 95% CI [1.24; 2.16]).

According to the HL test, the goodness of fit of the model was satisfactory ( $p = .39$ ).

**Table 2.** Anti-SARS-CoV-2 and influenza vaccine uptake either singularly or in co-administration in 2021/2022 and 2022/2023 campaigns by professional category.

	2021/2022		2022/2023		Percent change (%)	p-value
	N	N (%)	N	N (%)		
<b>Professional category</b>						
Physicians	1,227	85.68	470	32.82	-61.69	<.001*
Resident doctors	877	59.02	234	15.75	-73.31	<.001*
Nurses	1,741	81.09	206	9.59	-88.17	<.001*
Other HCWs	1,025	82.46	104	8.37	-89.84	<.001*
Administrative staff	837	76.72	161	14.76	-80.76	<.001*
Tot	5,707	77.13	1,175	15.88	-79.41	<.001*
<b>Professional category</b>						
Physicians	623	43.51	533	37.22	-14.45	<.001*
Resident doctors	414	27.86	260	17.50	-37.19	<.001*
Nurses	489	22.78	299	13.93	-38.85	<.001*
Other HCWs	282	22.69	161	12.95	-42.93	<.001*
Administrative staff	259	23.74	234	21.45	-9.64	.0823
Tot	2,067	27.94	1,487	20.10	-28.06	<.001*
<b>Professional category</b>						
Physicians	190	15.03	352	58.86	291.61	<.001*
Resident doctors	186	19.77	195	67.24	240.11	<.001*
Nurses	199	11.32	146	43.45	283.83	<.001*
Other HCWs	134	12.90	64	34.04	163.88	<.001*
Administrative staff	86	10.07	109	39.93	296.52	<.001*
Tot	795	13.58	866	51.39	278.42	<.001*

\*Statistically significant value.

**Table 3.** Total co-administration of anti-SARS-CoV-2 and influenza vaccines in 2021/2022 and 2022/2023 campaigns by age category.

Professional category	2021/2022		2022/2023		Percent change (%)	p-value
	N	N (%)	N	N (%)		
23-31	263	17.57	209	64.91	269.44	<.001*
32-41	182	13.97	164	52.23	273.87	<.001*
42-52	159	10.43	204	47.44	354.84	<.001*
53-84	191	12.47	289	46.69	274.42	<.001*
Tot	795	13.58	866	51.39	278.42	<.001*

\*Statistically significant value.

**Table 4.** Results of the multivariable logistic regression in form of odds ratio with 95% confidence intervals.

Variables	Odds ratio	95% CI	p-value
<b>Age category</b>			
23-31	1	[1; 1]	
32-41	0.83	[0.52; 1.32]	.427
42-52	0.79	[0.49; 1.27]	.328
53-84	0.67	[0.42; 1.07]	.091
<b>Sex</b>			
F	1	[1; 1]	
M	1.53	[1.23; 1.90]	<.001*
<b>Professional category</b>			
Physicians	1	[1; 1]	
Resident doctors	1.12	[0.69; 1.84]	.639
Nurses	0.65	[0.48; 0.87]	.004*
Other HCWs	0.37	[0.26; 0.53]	<.001*
Administrative staff	0.49	[0.37; 0.67]	<.001*
<b>Co-administration in 2021/2022</b>			
No	1	[1; 1]	
Yes	1.63	[1.24; 2.16]	.001*

\*Statistically significant value.

## Discussion

This study appears to be one of the first studies comparing co-administration across two vaccination campaigns among HCWs. HCWs represent a vital priority for vaccination due to their heightened exposure and substantial involvement in the transmission of infections within healthcare settings.<sup>20</sup> By interacting with a diverse

spectrum of individuals, they may unintentionally spread pathogens to already vulnerable patients, increasing the risk of severe complications.<sup>21,22</sup> Therefore, their immunization is crucial in safeguarding not just themselves but also their colleagues, and, most significantly, the most vulnerable patients.<sup>23</sup>

The findings of this study demonstrate a decrease in vaccination rates when compared to the 2021/22 season for both the anti-SARS-CoV-2 and influenza vaccinations, with reductions of 61% and 8%, respectively. However, despite this decline, there was a notable increase in co-administration adherence, with a rise of 38%.

The decline in the uptake of the second booster for the anti-SARS-CoV-2 vaccination could be attributed to several factors. Firstly, this dose was not mandatory for HCWs in Italy. Additionally, the Italian Government removed any obligation regarding SARS-CoV-2 vaccination on November 1, 2022.<sup>24</sup> Furthermore, with the end of the emergency period on March 31<sup>st</sup> 2022,<sup>25</sup> there was a decrease in vigilance against COVID-19. Lastly, many HCWs contracted the virus after receiving the first booster dose. At our hospital, approximately 1,994 (35%) HCWs were infected after receiving the first booster dose, and the risk of becoming ill increased as the weeks passed (cumulative risk of 2.5% at 4 weeks, 17% at 12 weeks, and 40% at 24 weeks).<sup>26,27</sup>

The negative trend in influenza vaccine coverage persists,<sup>28</sup> as highlighted in the previous campaign. This decline seems to be widespread, as it was also emphasized by Public Health England. In England, there was an 11.1% decrease in coverage between the 2021/2022 and the 2022/2023 season, making it the second consecutive season to witness a decrease in vaccination among HCWs, and the lowest uptake since the 2012/2013 season.<sup>29</sup> It is crucial to note that these declines are significant because they are compared to the 2020/2021 season when vaccination rates were very high due to the absence of the anti-SARS-CoV-2 vaccine and the fear that influenza symptoms could be mistaken for COVID-19.<sup>30</sup> Therefore, the observed coverage is quite similar to the rates achieved in the year before the pandemic.

The statistically significant increase in the practice of co-administration applies to all professional categories except for other HCWs. Existing literature shows that individuals who had previously received both vaccines concurrently expressed their willingness to do so in the future.<sup>6</sup> This awareness is further reinforced by effective, consistent, and frequent communication from public health authorities about the importance of receiving both vaccinations.<sup>4</sup> Additionally, studies have not reported any new or unexpected safety concerns, and the safety profile of each vaccine when administered alone aligns with published studies on co-administration of these vaccines.<sup>31</sup> Possibly, the organizational model adopted this year, consisting of five pairs of days between October and December, compared to the previous year when the vaccination center operated daily, has contributed to the increase in co-administration. In the previous year, approximately 1,200 healthcare workers administered both vaccines but on separate days, as they had the flexibility to visit the center daily and space out the two administrations.

The outcomes of the multivariable logistic regression are consistent with previous studies documented in the literature. Specifically, the acceptance of co-administration appeared to be higher among individuals directly engaged in patient care, particularly among physicians and resident doctors,<sup>32</sup> who exhibited a greater inclination toward vaccination.<sup>33–35</sup>

The impact of gender on vaccine acceptance remains a subject of debate, although there is evidence suggesting that females generally exhibit lower acceptance rates for both vaccines.<sup>36,37</sup> Nevertheless, further research is needed to assess the role of gender disparities in vaccination coverage.<sup>13</sup> Consistent with our findings, co-administration of vaccines was found to be more prevalent among male healthcare workers, with an adjusted OR of 1.53 CI 95% [1.23; 1.90].

On the contrary, the higher inclination of younger healthcare professionals toward co-administration seems atypical, as increasing age is typically linked to greater vaccine acceptance in existing literature.<sup>36,38,39</sup> Possibly, as suggested by Dominich et al.,<sup>13</sup> the lower acceptance of co-administration among older individuals could be attributed to their overall inclination to exercise greater caution when embracing novel technologies and healthcare practices: this stands out as an important sign of the cultural change taking place.

The joint reading of the study findings allows for a conceptual main implication. Specifically, the study findings raise policy implications across all levels of the decision-making process in the healthcare system. At the macro and meso level,

tailored vaccination policies should be issued to properly regulate the provision of vaccines within the healthcare services and to guarantee the related sustainability. Co-administration could be a great chance to reduce the number of vaccination sessions, the pressure on health facilities and, consequently, to decrease public health costs and, above all, augment vaccination uptake.<sup>4</sup> At the micro level, raising awareness about vaccine co-administration among HCWs is crucial not only to promoting good medical practices, but also to having knock-on benefits on patient education and having additional tools to hinder vaccine hesitancy. Therefore, HCWs play an essential role in influencing their patients' attitudes toward vaccination by motivating, reassuring, and convincing the population to get vaccinated, thereby contributing to public health protection.<sup>40,41</sup>

Moreover, the co-administration of vaccines for HCWs not only yields undeniable advantages in mitigating temporary productivity losses, due to potential side effects, thus ensuring the continuity of health care services and ultimately lowering costs for healthcare organizations.<sup>42–45</sup>

Overall, the study findings emphasize the importance of vaccination practice, especially in the hospital setting, in order to protect HCWs and patients and to ensure continuity of care.

These findings need to be assessed in light of their weaknesses and limitations. One limitation of this study is that it only considered workers who received vaccinations at our hospital. It is probable that numerous HCWs were vaccinated at alternative vaccination centers, general practitioner practices, or pharmacies. Furthermore, some workers over the age of 60 received their second booster dose with the monovalent vaccine as soon as it became available in July 2022. However, the study appears to be innovative as it compares data on the co-administration from two different vaccination campaigns (2021/2022–2022/2023). Another limitation is that the findings rely solely on data from a single hospital, potentially affecting the generalizability and introducing potential sources of bias. Nonetheless, it is worth noting that our hospital shares similar attributes with other national and international research hospitals. These characteristics include high levels of research engagement and a strong internal dedication to ensuring ongoing quality enhancement. Finally, it is important to note that the study did not consider a range of potential confounding factors related to vaccination acceptance. However, despite this limitation, the statistical analysis was conducted following appropriate methodological frameworks and the article considers the available evidence from the scientific literature.

Further investigations will be necessary to monitor the evolution of the trend of co-administration adherence in the forthcoming years, especially if ongoing anti-SARS-CoV-2 vaccination remains necessary. Additionally, conducting a survey to analyze the factors linked to adherence and hesitancy would be essential.

This study explores one aspect of a topic of growing importance and shows that the co-administration procedure, by virtue of its safety and simplification of logistics and organizational processes, is emerging as an effective tool in annual vaccination campaigns for SARS-CoV-2 and influenza. In the aftermath of COVID-19 pandemic, it is

vitally important to merge the insights garnered from the past few years with initiatives aimed at achieving efficient prevention, especially in high-risk environments such as hospitals.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

## Funding

The authors received no specific funding for this work.

## ORCID

Domenico Pascucci  <http://orcid.org/0000-0002-5804-2284>

## Author's contributors

DP, AL, LR, EM, MCN: Conceptualization and study design. DP and the AL acquired the data. DP and AL analyzed and interpreted the data. DP, AL and LR drafted the first version of the manuscript. All the authors critically revised and edited the manuscript. PL supervised the study.

## Data availability statement

The data are available upon request. All requests were addressed by the corresponding author.

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