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Safety profile and SARS-CoV-2 breakthrough infections among HCWs receiving anti-SARS-CoV-2 and influenza vaccines simultaneously: an Italian observational study

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ABSTRACT

In October/December 2021, World Health Organization and other international agencies recommended the offer of the third dose of anti-SARS-CoV-2 vaccine. In this period, the routine offer of seasonal influenza vaccination was also guaranteed and simultaneous administration of the two vaccines was encouraged.

This study aims to evaluate the safety profile and to estimate the incidence of SARS-CoV-2 breakthrough infections in subjects receiving the anti-SARS-CoV-2 and influenza vaccines simultaneously.

The study population was represented by healthcare workers (HCWs) of Bari Policlinico General Hospital who received the influenza (Flucelvax Tetra®) and/or anti-SARS-CoV-2 vaccination (BNT162b2 mRNA COVID-19 vaccine, Comirnaty®) either in coadministration or separately in October 2021. Reports of adverse events following immunization (AEFIs) were investigated to study the safety of both vaccines in coadministration and in separate-instance administration. Post-vaccination SARS-CoV-2 breakthrough infection was also studied.

942 HCWs accepted to join our study. 610/942 received both vaccines simultaneously. 25.26 % subjects (238/942) were only vaccinated against SARS-CoV-2, while the remaining 94 HCWs received the influenza vaccination first and subsequently received the anti-SARS-CoV2 booster dose.

717 HCWs reported AEFIs (Reporting Rate 76.1 per 100 subjects). Simultaneous administration of the two vaccines was not related with an increase of the rate of AEFIs compared to the single administration of SARS-CoV-2 vaccine, but the AEFIs' rate was lower among subjects who received only influenza vaccine.

Post-vaccination SARS-CoV-2 infections were notified for 41.5 % of enrolled subjects (391/942). Incidence of breakthrough infection and symptomatic disease was not significantly different between the simultaneous administration group and other subjects.

Our data suggests that simultaneous administration of a quadrivalent influenza vaccine and an mRNA anti-SARS-CoV-2 vaccine neither affected the safety of said products nor was associated with a higher risk of SARS-CoV-2 breakthrough infection.

1. Introduction

During the 2021/2022 fall-winter season, seasonal influenza vaccination overlapped with the anti-SARS-CoV-2 vaccination campaign. At the time, in fact, the booster dose of anti-SARS-CoV-2 mRNA vaccines had just been recommended for all healthcare workers (HCWs) by World Health Organization (WHO) [1], by the European Center for Disease Control and Prevention (ECDC) [2] and by Italian Healthcare Ministry circular 08 October 2021, n. 45886 [3]. This recommendation was motivated by the large-scale circulation of SARS-CoV-2 among HCWs; various 2020 and 2021 studies had identified positivity to serological SARS-CoV-2 tests even in personnel with no history of positive nasopharyngeal swabs [4], and a rapid decrease in the virus' circulation had been observed following the first phase of the anti-SARS-CoV-2 immunization program [5].

Although current guidelines recommend seasonal influenza

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vaccination for all HCWs [6], coverages in Italian hospitals are often inadequate [7], and the necessity of pushing the anti-SARS-CoV-2 vaccination campaign raised concerns about the possibility of a decline of anti-flu vaccination coverage. The simultaneous administration of the influenza and anti-SARS-CoV-2 vaccine was therefore suggested by WHO [8] and by Italian Healthcare Ministry circular 02 October 2021, n. 44591 [9]. This intervention also kept into consideration the fact that HCWs reported lack of time as one of the reasons for vaccine refusal [10], whereas simultaneous administration requires a single access and concentrates possible adverse events following immunization (AEFIs) in a limited period.

Vaccine coadministration is a practice characterized by well-known safety and effectiveness, as children usually receive multiple vaccines during the same immunization session. Various studies have demonstrated the noninferiority of simultaneous administration in terms of efficacy/effectiveness and safety for various vaccines, including the newly released anti-SARS-CoV-2 ones, both in children and in the adult [11–15]. In addition to this, the simultaneous administration of influenza and anti-SARS-CoV-2 vaccines is currently recommended by the United States Advisory Committee on Immunization Practices [16]. It should however be noted that the safety of these products' simultaneous administration was only investigated in small studies, and evidence regarding effectiveness is currently lacking.

Our study describes data concerning safety and incidence of breakthrough infection gathered from the observation of a cohort of HCWs who underwent influenza and anti-SARS-CoV-2 vaccination, either separately or in coadministration. Our aim is to define whether the coadministration of these products preserves the safety profile of both vaccines and the capacity of mRNA anti-SARS-CoV-2-vaccines to prevent the infection and symptomatic COVID-19.

2. Materials and methods

2.1. Study design and population

This is a prospective observational study. It was preemptively notified to and approved by the Ethics Committee of Bari Policlinico General Hospital, and it was carried out in accordance with the Helsinki Declaration.

Bari Policlinico General Hospital is the largest hospital in Southern Italy. It has fifty operative units (OUs) and can host over a thousand patients, and its personnel counts over six thousand HCWs. Since October 12th, 2021, Bari Policlinico's Hygiene department has set up an ad-hoc vaccination clinic offering influenza vaccination and anti-SARS-CoV-2 booster to all HCWs operating in Policlinico's facilities. The clinic was open ten hours a day, Mondays to Saturday, and an appointment was not required. At the same time, the Hygiene department also started an on-site vaccination offer targeting most of the hospital's OUs [17]. The staff employed in both the vaccination clinic and the on-site service was made of Public Health physicians with expertise in vaccinology, as well as residents from Policlinico's Public Health post-graduate School.

HCWs attending the clinic and/or the on-site service were able to choose whether to receive only one of the two vaccines or both.

The study population was therefore represented by all HCWs who attended said vaccination services from October 12th to October 22nd, 2021, receiving influenza (Flucelvax Tetra®) and/or anti-SARS-CoV-2 (BNT162b2 mRNA COVID-19 vaccine, Comirnaty®) vaccination either in simultaneous administration or separately and accepting to take part in a retrospective surveillance program. Subjects who received influenza or anti-SARS-CoV-2 vaccines other than the ones mentioned above were not included.

2.2. Adverse event surveillance and classification

Participants were provided a paper-based clinical diary in order to take daily notes of any adverse events occurring after vaccination; a copy of the diary itself is provided among the Supplementary materials (Attachment 1), together with an English-translated version of it (Attachment 2). One week after the vaccination, each subject was contacted via phone call by Public Health post-graduate School residents, and an interview was carried out to collect the information noted on the diary and assess any AEFIs occurred during this period. Adverse events were then notified to hospital's pharmacovigilance service, as per directives of the European Union on adverse event surveillance, and subsequently registered into the Italian Drug Authority's (AIFA) National Pharmacovigilance Network database [18].

AEFIs were classified as serious or non-serious according to WHO guidelines. Adverse events were defined as serious when resulting in death, hospitalization or prolongation of existing hospitalization, persistent and/or significant disability/incapacity, congenital anomalies or birth defects, when posing a threat to the subject's survival or when requiring intervention to prevent permanent impairment or damages [19]. Additionally, AEFIs listed among "special interest health conditions" according to the European Medicines Agency (EMA) and AIFA were considered as serious adverse events as well [20,21].

2.3. Effectiveness analysis

Effectiveness of the anti-SARS-CoV-2 vaccine was studied by collecting information about SARS-CoV-2 infections occurred from November 1st, 2021, to June 30th, 2022; only infections occurring at least 14 days after the vaccine's administration were taken into consideration (breakthrough infections), and a 280-day follow-up was performed for all subjects after the recorded date of anti-SARS-CoV-2 vaccination (including group 3, in which data regarding SARS-CoV-2 vaccination was collected retrospectively). Data was collected from Puglia Region's Regional Integrated Online Epidemiological Database (IRIS), which contains all medical reports regarding SARS-CoV-2 diagnostic tests. For context, HCWs have been routinely screened for SARS-CoV-2 infection in the study hospital via antigenic test, performed in the hospital's sample collection center once a month. However, both antigenic and Polymerase Chain Reaction-based molecular tests were considered valid in order to identify breakthrough infections. HCWs who tested positive to SARS-CoV-2 after receiving the booster dose were contacted by the Hygiene department's personnel and an interview was carried out on the phone. During this interview, the following information was collected:

- Symptoms reported during the after-vaccination SARS-CoV-2 infection (for subjects who tested positive for SARS-CoV-2 after the vaccine's administration) and duration of the COVID-19 symptoms.
- Hospitalization required during the after-vaccination infection.

A database was built containing the participants' personal data, information reported in the post-vaccination follow-up and, for symptomatic COVID-19 cases, information about the symptoms' duration and required hospitalization.

2.4. Statistical analysis

An Excel® spreadsheet was used to structure the database, and statistical analysis was carried out via software STATA MP17®.

Continuous variables were expressed as means ± standard deviations and range. Categorical variables were described as percentages.

Reported AEFIs were grouped into the following categories:

- Local reactions (pain, redness, swelling, induration at the injection site).
- Allergic reactions (anaphylaxis, allergic/urticarial reactions).
- Gastrointestinal symptoms (nausea, vomiting, diarrhea).
- General malaise (asthenia, malaise, myalgia/arthralgia).

- Neurological symptoms (drowsiness/insomnia, irritability, nervousness, headache).
- Fever/hyperpyrexia and chills.

Reporting rates were calculated as number of reports of adverse events/number of recruited subjects; the resulting proportion was multiplied by 100.

According to the two vaccines' administration time, participants to the survey were divided into three groups: subjects who received the booster dose of the anti-SARS-CoV-2 vaccine in simultaneous administration with influenza vaccine (group 1); subjects who received only the SARS-CoV-2 vaccine booster dose (group 2); subjects who received the influenza vaccination and delayed the anti-SARS-CoV-2 booster dose's administration after the 22nd of October 2021 (group 3). Group 2–3 is therefore comprised of subjects who did not receive simultaneous administration.

Participants were divided into two groups according to the median age of participants (51 years) at the time of vaccination.

Categorical variables of the three groups were confronted via Chi-square test. The proportions of AEFIs between groups of interest were compared via McNemar's test, and the Odds Ratio for reporting AEFIs between different groups was calculated. A logistic multivariable regression model was built in order to analyze the correlation of adverse event occurrence with sex, age and simultaneous administration of influenza and anti-SARS-CoV-2 vaccines.

Incidence rates per 100 follow-ups of infection and of disease were both estimated, including 95 % confidence intervals (95 %CIs). The incidence rate ratio between group 1 and group 2–3 and its 95 %CI were also calculated both for SARS-CoV-2 breakthrough infection and for breakthrough COVID-19.

A logistic multivariable regression model was built in order to analyze the correlation of either diagnosis or symptomatic infection with sex, age and simultaneous administration of influenza and anti-SARS-CoV-2 vaccines. Finally, a linear multivariable regression model was built to analyze the correlation of the symptoms' duration with the subject's age, sex and simultaneous administration.

The Kaplan-Meier method was used to estimate the cumulative incidence of infection diagnosis with nasopharyngeal swab and symptomatic SARS-CoV-2 breakthrough infection, both for Group 1 and Group 2–3.

For all tests, a two-sided p-value < 0.05 was chosen as a break point for statistical significance.

3. Results

From October 12th to October 22nd, 2021, 1038 HCWs were vaccinated against influenza, SARS-CoV-2, or both. 942 accepted to join our study (response rate 90.8 %).

Group 1 represented 64.76 % of the study population (610/942). 25.26 % of the HCWs (238/942) belonged to group 2, while the remaining 9.98 % (94/942) were part of group 3. The characteristics of each group are summarized in Table 1, while Graph 1 resumes each group's vaccination course. As already stated, the population's median age was 51 years, with 462 subjects younger than 51 and 480 subjects 51 or older.

Table 1
Characteristics of the three study groups.

	Group 1 (n = 610)	Group 2 (n = 238)	Group 3 (n = 94)	Total (n = 942)	p-value
Age	49.06 ± 12.90 (20–78)	48.57 ± 11.76 (21–69)	49.78 ± 11.37 (25–68)	49.01 ± 23.47 (20–78)	0.7103
Males	278 (45.57 %)	85 (35.71 %)	36 (38.30 %)	399 (42.36 %)	0.0233
Females	332 (54.43 %)	153 (64.29 %)	58 (61.70 %)	543 (57.64 %)	

3.1. Safety

717 HCWs out of 942 reported at least one adverse event (reporting rate 76.11 per 100 follow-ups); out of these subjects, 388 were under 51 years of age, while the remaining 329 were older.

Logistic regression showed a significantly lower odd of adverse events for subjects older than 50 (OR = 0.45; 95 %CI = 0.32–0.61; $p < 0.001$) and for males (OR = 0.52; 95 %CI = 0.38–0.71; p-value < 0.001). There was no significant increase in the odd of AEFIs in subjects receiving the anti-SARS-CoV-2 vaccination alone when confronted with those in the simultaneous administration group (OR = 1.07; 95 %CI = 0.73–1.57; p-value = 0.71). On the other hand, a significantly lower odd of adverse events was observed in subjects who had only received the anti-flu vaccination confronted with the simultaneous administration group (OR = 0.35; 95 %CI = 0.22–0.55; p-value < 0.001).

For Group 1, 474 HCWs reported an AEFI out of 610 (reporting rate 77.70 %); for Group 2, 190 out of 238 (reporting rate 79.83 %); for Group 3, 53 out of 94 (reporting rate 56.38 %). Reporting rates were not different between Group 1 and Group 2 ($p > 0.05$), whereas Group 3 showed a reporting rate lower than the other two groups ($p < 0.001$).

For Group 1, 262/304 younger subjects (<51-year old) reported an AEFI (reporting rate 86.18 %), while 212/306 older subjects (≥51-years old) reported an AEFI (reporting rate 69.28 %), highlighting a protective effect of older age (OR = 0.36; 95 %CI = 0.23–0.55; $p < 0.001$); for Group 2, 99/117 younger subjects reported an AEFI (reporting rate 84.62 %), while the percentage among older subjects was 91/121 (reporting rate 75.21 %) (OR = 0.55; 95 %CI = 0.27–1.10; p = 0.07). For Group 3, 27/41 younger subjects reported an AEFI (reporting rate 65.85 %), while the percentage was 26/53 among older subjects (reporting rate 49.06 %) (OR = 0.50; 95 %CI = 0.20–1.25; p = 0.10).

For Group 1, 277/322 women (reporting rate 83.43 %) and 197/278 (reporting rate 70,86) men reported an AEFI (OR = 0.48; 95 %CI = 0.32–0.72; $p < 0.001$).

For Group 2, reporting rate was 86.93 % (133/153) among women and 67.06 % among men (57/85) (OR = 0.30; 95 %CI = 0.15–0.62; $p < 0.001$) and for Group 3, 56.90 % (33/58) among women and 55.56 (20/36) among men (OR = 0.95; 95 %CI = 0.38–2.39; p = 0.90).

No AEFI was classified as serious.

For HCWs who reported one or more AEFIs, symptoms began within the first 48 h after vaccination in 97.47 % of cases in Group 1, 99.47 % of cases in Group 2, and 96.23 % of cases in Group 3. In a similar manner, 59.49 % of Group 1, 60.23 % of Group 2, and 54.72 % of Group 3 HCWs signaled that their symptoms were fully resolved over 96 h from the vaccination. All adverse events had undergone full resolution before the end of the week after the vaccine administration.

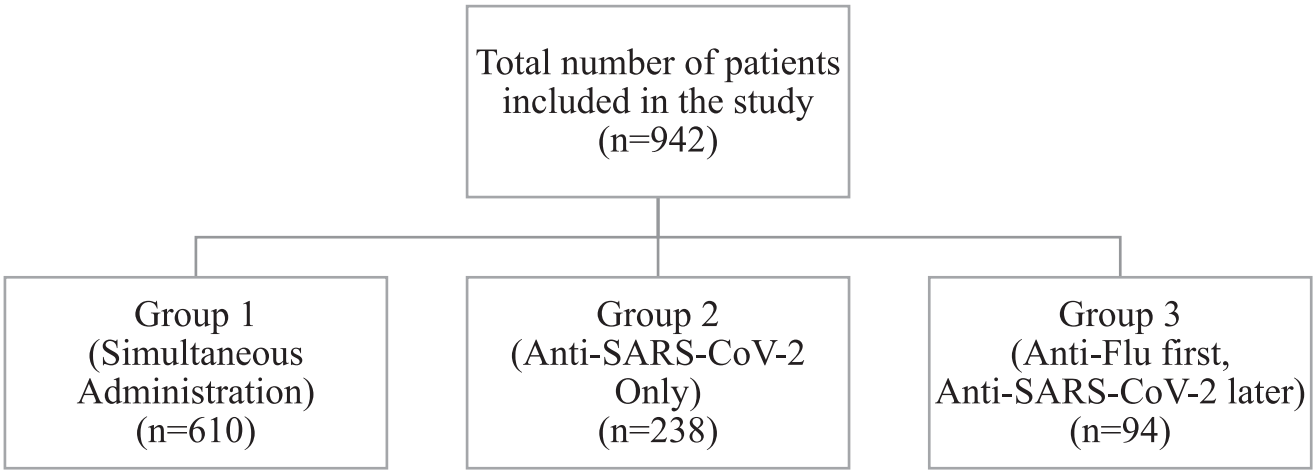
Further information regarding AEFIs' reporting rate by group and type of symptoms is reported in Table 2.

3.2. Breakthrough infections

A post-vaccination SARS-CoV-2 breakthrough infection during the 280-day follow-up period was notified for 41.5 per 100 subjects (391/942; 95 % CI: 38.36–44.65).

Incidence was 40.00 per 100 subjects (244/610; 95 % CI = 36.11–43.89) among Group 1, 44.96 per 100 follow-upped people (107/238; 95 % CI = 38.64–51.28) in Group 2 and 42.55 per 100 follow-upped people (40/94; 95 % CI = 32.56/52.55) in Group 3 (p = 0.41); overall, among Group 2 and 3, the incidence was 44.28 per 100 follow-ups (147/332; 95 % CI = 38.93/49.62) and seemed not different than figure from Group 1 (Incidence Rate Ratio = 0.90; 95 %CI = 0.73 – 1.12, p = 0.20).

The average time from vaccination to the diagnosis of SARS-CoV-2 infection was 140.6 ± 53.4 days (range 31–273 days). For group 1, the mean time was 141.71 ± 50.05 days, while for group 2 and 3 it was



Graph 1. Study population distribution among groups.

Table 2
AEFIs reporting rate (x100 follow-up), by group and by type of symptoms.

		Group1	Group2	Group3	Overall	
AEFIs reporting rate		77,70	79,83	56,38	76,11	0,001
AEFIs reporting rate by type of symptoms	Local reactions	56,72	51,68	42,55	54,03	0,026
	General malaise	38,85	42,44	20,21	37,90	0,001
	Fever/hyperpyrexia	17,05	22,69	6,38	17,41	0,002
	Neurological symptoms	13,44	13,87	3,19	12,53	0,016
	Gastrointestinal symptoms	3,44	2,52	2,13	3,08	0,669
	Allergic/Urticarial reaction	0,33	0,84	0,00	0,42	0,470

138.75 ± 58.63 days ($p > 0.05$).

82.6 % (323/391) of enrolled subjects with breakthrough SARS-CoV-2 infection reported suffering from one or more COVID-19-related symptoms. When symptoms were reported, their mean duration was 6.2 ± 4.9 days (range 1–21 days). Only one HCW required hospitalization due to COVID-19.

The incidence of symptomatic SARS-CoV-2 infection was 32.62 per 100 follow-upped people (199/610; 95 % CI = 28.90–36.34) among Group 1, 37.82 per 100 follow-upped people (90/238; 95 % CI = 31.65–43.98) in Group 2 and 36.17 per 100 follow-upped people (34/94; 95 % CI = 26.46–48.88) in Group 3 ($p = 0.33$); overall, among Group 2 and 3, the incidence was 37.35 per 100 follow-upped people (124/332; 95 % CI = 32.15–42.55) and seemed not different than figure from Group 1 (Incidence Rate Ratio = 0.87; 95 %CI = 0.69–1.10; $p = 0.14$).

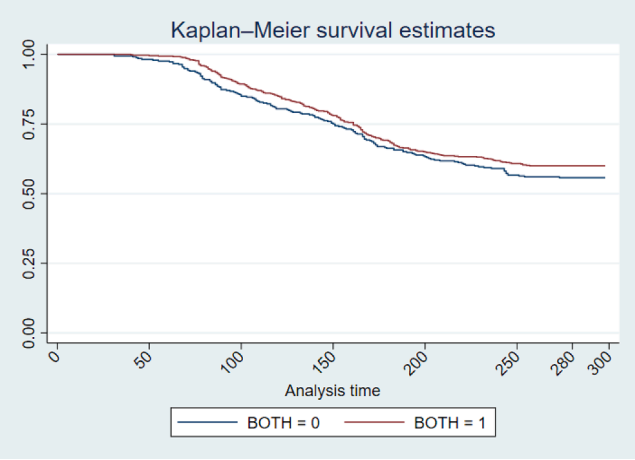
3.3. Regression model

Following logistic multivariable regression, the association of simultaneous administration with the probability of getting infected and being symptomatic was not statistically significant (p-value > 0.05). Male sex and older age, on the contrary, were significantly associated with a lower probability of being infected (OR for male sex: 0.98; OR for older age: 0.72) and having symptoms (OR for male sex: 0.97; OR for older age: 0.74) (p-value < 0.05).

In Graph 2 we reported the Kaplan-Meier survival curve for subjects who received the anti-SARS-CoV-2 vaccine in simultaneous administration with influenza vaccination versus those who were administered with the anti-SARS-CoV-2 vaccine only. It is evident that the two curves are mostly overlapping. Similar results were observed when only symptomatic infections were considered, as seen in Graph 3..

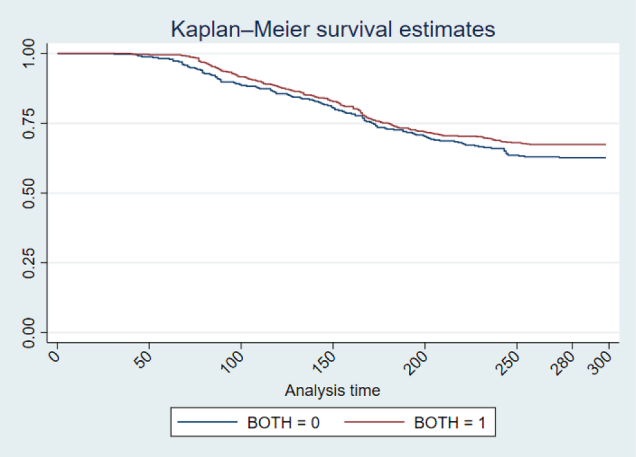
3.4. Symptoms' duration

When breakthrough COVID-19 was diagnosed, symptoms had a mean duration of 6.34 ± 5.29 for Group 1 and 6.00 ± 4.42 for Group 2–3.



Graph 2. Kaplan-Meier survival curve for subjects who received the anti-SARS-CoV-2 vaccine alone (blue curve) and in simultaneous administration with the influenza vaccine (red curve). The end point of the survival curve is the infection diagnosis with nasopharyngeal swab. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The linear multivariable regression model showed that the symptomatic period was significantly longer in females than males (coefficient = +1.30 days; $p < 0.05$) and in older HCWs (coefficient = +0.06 days per year of age; $p < 0.05$). On the other hand, simultaneous administration of the vaccines was not associated with a significant difference in terms of symptoms' duration ($p > 0.05$).



Graph 3. Kaplan-Meier survival curve for subjects who received the anti-SARS-CoV-2 vaccine alone (blue curve) and in simultaneous administration with the influenza vaccine (red curve). The end point of the survival curve is symptomatic SARS-CoV-2 infection. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

During the study period, 942 healthcare providers working at Bari Policlinico general hospital were vaccinated against influenza, SARS-CoV-2, or both. Most subjects (610/942) accepted to receive the two vaccines in simultaneous administration, while 238 chose to undergo anti-SARS-CoV-2 vaccination alone and 94 remanded the booster dose of this vaccine and only received the influenza vaccine.

No significant differences were observed in terms of safety between the anti-SARS-CoV-2-only group and the simultaneous administration group, while a significantly higher number of adverse events were reported in the latter in comparison with the influenza-only group. This difference was likely due to the different reactogenicity of the two products: by confronting studies conducted on Comirnaty® [22,23] with others regarding Flucelvax Tetra® [24–26], it is apparent that the former has greater tendency to cause adverse events. Therefore, it is reasonable to assume that the greater number of AEFIs in the simultaneous administration group was caused by the presence of the anti-SARS-CoV-2 vaccine rather than by simultaneous administration itself.

Local reactions, malaise and fever were the most common adverse events in the study population. Pre-marketing evidence reported similar data, stating that injection site pain, erythema and induration, fatigue, myalgia and headache were very common AEFIs for Flucelvax Tetra®, with a frequency ranging from 10 % to 34 % [27]. Pre-licensure information about Comirnaty® is mostly alike, reporting high frequency of local pain (>80 %), fatigue (>60 %), headache (>50 %), myalgia (>40 %), chills (>30 %), arthralgia (>20 %), pyrexia and injection site swelling (>10 %) [28]. This data also confirms what was stated above about the two products' different reactogenicity profile.

No differences were highlighted in the incidence of breakthrough infections and symptomatic disease between the simultaneous administration group and the others. This data suggests that there are no significant interactions between Comirnaty® and Flucelvax Tetra®, thus supporting their contemporary use.

Despite being a relatively new field, simultaneous administration of anti-SARS-CoV-2 vaccines with other immunization products has already been investigated in terms of safety and efficacy by other studies. An exploratory phase 3 trial by Toback et al. showed that the humoral response to neither trivalent adjuvanted nor quadrivalent influenza vaccines is affected by simultaneous administration with adjuvanted anti-SARS-CoV-2 vaccine NVX-CoV2372. On the other hand, a modest reduction in the anti-spike protein IgG ELISA units was observed with the simultaneous administration of NVX-CoV2372 with an influenza vaccine. Due to the absence of a correlate of protection, though, the authors admitted that the significance of this data was difficult to establish [29].

A phase 2 study by Izikson et al. focused on the preservation of a high-dose quadrivalent influenza vaccine's safety and immunogenicity when administered with a third dose of the mRNA-1273 anti-SARS-CoV-2 vaccine in over-65 patients. Izikson's paper highlighted that the safety and immunogenicity profiles of the quadrivalent influenza vaccine appeared to be conserved for the simultaneous administration group, but did not research into the preservation of mRNA-1273's safety and efficacy, mainly due to the lack of information about correlates of protection [30].

Our study's main strength is represented by its post-marketing design. To our knowledge, no other paper has investigated the effectiveness of either influenza or anti-SARS-CoV-2 vaccines when in simultaneous administration so far. Available studies were limited to these vaccines' immunogenicity, which was measured in terms of antibody titers [29,30]. In fact, previous research consisted of clinical pre-marketing studies on low-numerosity pre-selected populations. Our study was carried out on a significantly larger sample which was not filtered before enrolment, and retrospectively investigated the breakthrough infection incidence by contacting each subject after a significant amount of time.

Another valuable asset was represented by the active AEFI surveillance system we employed. It is currently known that passive surveillance tends to cause under-reporting of adverse events and alters the serious/non-serious adverse events ratio, while active data collection is able to increase the quality of gathered information and the causal association analysis [31–33].

Our main weakness, on the other hand, is represented by the lack of information regarding Flucelvax Tetra®'s effectiveness when administered with an anti-SARS-CoV-2 vaccine. It should be kept into consideration, however, that while data about SARS-CoV-2 infections are easily available due to routine screening policies in HCWs employed in Italy, the incidence of ILI is generally underestimated, making it difficult to effectively appraise seasonal vaccination's VE [34–36].

Another flaw in our study is the fact that information about the anti-SARS-CoV-2 vaccine's effectiveness could not be gathered. In fact, we could not investigate the incidence of SARS-CoV-2 infection in a non-vaccinated population, thus rendering the calculation of the product's effectiveness impossible. Further, the study population is unfortunately smaller than desirable as far as safety analysis is concerned. In fact, we did not manage to enroll >1,000 subjects, thus making it impossible to define the frequency of rare adverse events. Since our study was hospital-centered, however, it would have been impossible to increase its size.

In addition, a certain degree of bias could have been caused by the non-random distribution of groups, as HCWs choosing a single vaccination over simultaneous administration of the two vaccines may have been prone to minimize side effects, leading to underreporting. Finally, despite our sample being representative of the real-world scenario of a large Southern Italy hospital, it is far less representative as far as non-HCWs are concerned. It would be interesting for future research to focus on wider population groups, taking into consideration other factors such as comorbidities, current employment and living environment in order to verify whether they influence the incidence of breakthrough infections [37–40].

5. Conclusions

Our data shows that simultaneous administration of a quadrivalent influenza vaccine and an mRNA anti-SARS-CoV-2 vaccine is not inferior to the single vaccines administration in terms of safety. We also observed no significant differences in the incidence of SARS-CoV-2 breakthrough infections comparing subjects who received the simultaneous

administration of the two vaccines and subjects who received the single administration of anti-SARS-CoV-2 vaccine.

Author contributions

LM and VV are joint first authors.

Contributors study design: VV, LM, PS and ST. Data gathering and manuscript editing: VV, ADL, FT and FV. Data analysis: AM, ADL and ST. Supervision: PS and ST.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.07.043.

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