Human Vaccines & Immunotherapeutics

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/khvi20

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To cite this article: Pasquale Stefanizzi, Silvio Tafuri & Francesco Paolo Bianchi (2022) Immunogenicity of third dose of anti-SARS-CoV-2 vaccine co-administered with influenza vaccine: An open question, Human Vaccines & Immunotherapeutics, 18:6, 2094653, DOI: 10.1080/21645515.2022.2094653

To link to this article: https://doi.org/10.1080/21645515.2022.2094653

Published online: 12 Jul 2022.

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 6, e2094653 (3 pages)
https://doi.org/10.1080/21645515.2022.2094653

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Immunogenicity of third dose of anti-SARS-CoV-2 vaccine co-administered with influenza vaccine: An open question

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ABSTRACT

In October 2021, the Italian Ministry of Health has planned the offer of a booster dose of anti-SARS-CoV-2 vaccine for healthcare workers (HCWs), recommending the simultaneous administration of the third anti-SARS-CoV-2 dose and the influenza vaccine. The immunogenicity and serological response of co-administration are questioned. This is a retrospective cohort pilot study. We evaluated in a sample of HCWs the serological response 1 month after the administration of the third dose, comparing it between subjects who chose for co-administration (Cominarty+Flucelvax) and subjects who preferred the administration of the anti-SARS-CoV-2 vaccine. The study population comprised 20 HCWs, 9 (45.0%) chose co-administration (Group 1), and 11 (55.0%) preferred the administration of the COVID-19 vaccine alone (Group 2). A statistical significant difference of the variation of IgG anti-spike-protein antibodies between the serological evaluation at 1 month after the third dose and the serological evaluation 1 month after the basal routine with Comirnaty between Group 1 (−4,842.9; 95%CI = −15,799.2–6,113.2) and Group 2 (9,258.9; 95%CI = 1,081.0–17,435.9; *p*-value = 0.029) was reported. New scientific evidences are necessary to clarify this critical issue to guarantee both the best immunogenicity of COVID-19 vaccination and an high vaccine coverage for influenza vaccination.

ARTICLE HISTORY
Received 26 April 2022
Revised 20 June 2022
Accepted 23 June 2022

KEYWORDS
COVID-19; influenza; immunogenicity; booster dose; healthcare workers

Introduction

To deal with the COVID-19 pandemic, a mass vaccination campaign was started in European countries on 27 December 2020. In Italy, healthcare workers (HCWs) were a priority target group for vaccination offer.[1]

In fall 2021, the European Center for Disease Control and Prevention (ECDC) recommended proposing a booster dose for individuals who have already received a complete vaccination routine but still remain at high risk of virus exposure,[2] such as healthcare providers.[3] Subsequently, in October, 2021, the Italian Ministry of Health has deliberate the proposal of a third booster dose of anti-SARS-CoV-2 vaccine for HCWs; the guidelines suggested the concurrent administration of the third anti-SARS-CoV-2 and the influenza vaccines.[4,5]

Those recommendations were fundamental from a Public Health viewpoint; this policy permitted the active offer of the third dose of anti-SARS-CoV-2 vaccine, avoiding the chance of missing influenza vaccine shot. In the last seasons, influenza vaccine coverage in the Italian health personnel was generally suboptimal[6]; nevertheless, COVID-19 pandemic increased influenza immunization adherence, reaching highest coverage in 2020/21 season.[7] Even if co-administration is reported to be a concerning issue for health personnel, due to the fear of adverse reactions,[8] the strategy of co-administration of anti-SARS-CoV-2 and flu vaccines could represent a main policy to strengthen the results achieved in the previous influenza vaccine campaign, as the third booster dose represented an appropriate circumstance to increase the willingness to the flu vaccine.

Bari Policlinico University Hospital (Southern Italy, Apulia, almost 4,000,000 citizens) offered the concurrent administration of anti-SARS-CoV-2 and flu vaccines; as reported by a 2021 study of our research team,[9] in the first 2 weeks of immunization campaign (October 12–24, 2021), 2,740 (45.7%) healthcare providers accessed the vaccination clinic at Hygiene department and 1,643 (60.0%) chose concurrent administration of the two vaccines. Willingness of co-administration was better among health personnel directly involved in patient care, as well as physicians and residents of Medical school.

On our knowledge, studies that assessed the immunogenicity and serological response of co-administration of COVID-19 vaccines with influenza vaccines are not reported in literature, except for a few experience published in the last months.[10–12]

Materials and methods

This is a retrospective cohort pilot study. In our hospital, periodical serosurvey of immunized personnel are carried out. So, we evaluated in a small sample of HCWs the serological response one month after the administration of the third dose, comparing it between subjects who chose for co-administration (Cominarty + Flucelvax) and subjects who preferred the administration of the anti-SARS-CoV-2 vaccine first (Comirnaty). We evaluated the variation of IgG anti-spike-protein antibodies between the serological evaluation at 1 month after the third dose and the serological evaluation 1 month after the basal routine with Comirnaty.

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The manuscript has not been presented at a meeting.

The presence of specific IgG anti-spike-protein antibodies was assessed using the Abbott IgG quantitative test. This automated, two-step chemiluminescent microparticle immunoassay) allows qualitative and quantitative determinations of IgG antibodies to SARS-CoV-2 in human serum and plasma. The blood sample was incubated with SARS-CoV-2-antigen-coated paramagnetic microparticles and assay diluent. Anti-SARS-CoV-2 IgG antibodies present in the sample bind to the microparticles. After a washing step, anti-human IgG acridinium-labeled conjugate was added and the mixture is incubated again. Following a second wash cycle, pre-trigger and trigger solutions were added. The resulting chemiluminescent reaction was measured in relative light units, which can be directly related to the amount of IgG antibodies to SARS-CoV-2 in the sample. A four-parameter logistic curve fit data reduction method (y-weighted) was used for calibration and sample determinations. The cutoff was 50.0 AU/mL.

The dataset was created as an Excel spreadsheet that included information on sex, age, and serological data at each detection time. An anonymized data analysis was performed using STATA MP17 software. Continuous variables are reported as the mean ± standard deviation and range and categorical variables as proportions. The results of the serological analysis are expressed as the geometric mean titer (GMT) and its 95% confidence interval (9%%CI). Continuous variables were compared between group with t student test for independent data. For all tests, a two-sided p-value <0.05 was considered to indicate statistical significance.

Results

The study population comprised 20 HCWs, of which 11 (55.0%) females, with a mean age of 30.5 ± 4.7 years (range = 24–41); 9 (45.0%) chose co-administration (Group 1); and 11 (55.0%) preferred the administration of the COVID-19 vaccine alone (Group 2). Any of the enrolled subjects reported a history of COVID-19 disease. The median interval between the second and third vaccine doses was 290.5 days (interquartile range = 269–299). The baseline value of IgG anti-SARS-COV-2 geometric mean titer (GMT) was of 18,333.8 (95%CI = 12,571.8–26,736.6) in Group 1 and 10199.8 (95%CI = 3,906.4–26,631.7) in Group 2. After the third dose, all subjects resulted seroprotected, with a GMT of 14132.5 (95%CI = 8,144.0–24,542.4) and in particular 12343.2 (95%CI = 7,137.7–26,736.6) in Group 1 and 15787.7 (95%CI = 5,829.7–42,755.8) in Group 2. Considering the variation of IgG anti-spike-protein, we found a mean increase of circulating antibodies equal to 2,913.0 (95%CI = −3,954.6–9,780.6); anyway, a statistical significant difference of the variation between Group 1 (−4,842.9; 95%CI = −15,799.2–6,113.2) and Group 2 (9,258.9; 95%CI = 1,081.0–17,435.9; p-value = 0.029) was reported.

Discussion

The results of our study must be read from the perspective of a very small sample with a low mean age and a missing randomization of enrolled subjects, which are major limitations; hence the current study needs confirmation in an expanded study. A few clinical trial investigated this topic, Toback S et al.[10] developed a phase III efficacy RCT, in which a first dose of NVX-CoV2373 (Nuvaxovid, Novavax) plus influenza vaccine (QIVc, aTIV) or influenza vaccine alone; reactogenicity events were more common in the co-administration group than in the NVX-CoV2373 alone group and co-administration resulted in no change to influenza vaccine immune response although a reduction in antibody responses to the NVX-CoV2373 vaccine was noted. A randomized clinical trial compared (1) receiving a second dose of mRNA-1273 (Spikevax, Moderna) plus a high-dose quadrivalent influenza vaccine (QIV-HD; Fluzone High-Dose Quadrivalent, Sanofi Pasteur), (2) a dose of QIV-HD alone, or (3) a second dose of mRNA-1273 alone in older adults (≥65 years); the authors concluded that no safety concerns or immune interference were observed for concomitant administration of QIV-HD with mRNA-1273 booster, supporting co-administration recommendations.[11] A phase IV trial conducted in the UK reporting the coadministration of either a second dose of ChAdOx1 (AstraZeneca) or BNT162b2 vaccines, together with influenza vaccine (QIVr Supemtek, Sanofi Pasteur) for subjects aged 18–64 years or an adjuvanted trivalent influenza vaccine (aTIV; Fluad, Seqirus) for those aged ≥65 years) or ChAdOx1/BNT162b2 together with placebo; also in this case, the authors concluded that the concomitant vaccination with ChAdOx1 or BNT162b2 plus an age-appropriate influenza vaccine raises no safety concerns and preserves antibody responses to both vaccines.[12] A 2022 paper[13] systematically reviews the studies on the topic, concluding that that the humoral IgG response measured by means of the hemagglutination inhibition assay toward any seasonal influenza vaccination (SIV) strain is preserved in COVID-19 + SIV co-administration groups and that the immune response toward four influenza strains and the SARS-CoV-2 spike protein in co-administration groups is generally non-inferior to that seen in groups receiving either vaccine alone.

In summary, the above reported studies suggested that the co-administration of influenza and COVID-19 vaccines did not influence the humoral response. Future studies should consider larger sample size, and data should be stratified per many covariates (age class, sex, comorbidities, etc.). New scientific evidences (especially phase IV studies) are necessary to clarify this critical issue; in this way, international and national Public Health institutions should update guidelines to guarantee both the best immunogenicity of COVID-19 vaccination and an high vaccine coverage for influenza vaccination, in particular for high risk group in which the optimal immunogenicity of the COVID-19 vaccines must be reached.

Acknowledgements

The authorse acknowledge Mr. Nazario Brescia for the copy-editing of this paper.

Disclosure statement

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

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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