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Safety and immunogenicity of synchronous COVID19 and influenza vaccination

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ABSTRACT

Given the ongoing COVID19 pandemic, the decline in serological response since dose 2, and the upcoming flu season, COVID19 vaccines will increasingly be administered in combination with vaccines against seasonal pathogens. It is of interest to confirm that concurrent vaccination against influenzavirus has no negative impact on serological response to SARS CoV-2.

Anti-Spike IgG and Anti-Receptor Binding Domain (RBD) Neutralizing Antibodies (NAb) in serum was assessed in 64 immunocompetent healthcare workers (HCW) before and 14 days post the third dose of BNT162b2 vaccine (Comirnaty®, Pfizer/BioNTech) or BNT162b2 plus quadrivalent flu vaccine (Vaxigript Tetra ®Sanofi Pasteur) on the same day.

We report here safety and efficacy of combined BNT162b2 and flu vaccine in 64 healthcare workers at a single institution. No differences were found in adverse events or anti-Spike antibody levels.

Introduction

Combining vaccinations against different pathogens has been standard practice for decades in both pediatric and adult patients. Considering the 2021/2022 influenza season, several countries have begun to offer boost doses of COVID19 vaccines [1,2,3]. This can be done either alone or in combination with other vaccines such as influenza [4]. Given the ongoing COVID19 pandemic (and the decline in serological response since dose 2) and the upcoming flu season, it is of interest to confirm that concurrent vaccination against influenzavirus has no negative impact on serological response.

Methods

In this study, 64 immunocompetent healthcare workers (HCW) employed within the Varese Hospital voluntarily choose to get only the third dose of BNT162b2 vaccine (Comirnaty®, Pfizer/BioNTech) or BNT162b2 plus quadrivalent flu vaccine (Vaxigript Tetra ®Sanofi Pasteur) on the same day (different upper arms). All HCW had previously received a second dose of BNT162b2 9-10 months before, and only 4 of them previously had symptomatic SARS-CoV-2 infection before the first BNT162b2 dose. Anti-Spike IgG were assessed with Liaison SARS-CoV-2 TrimericS IgG assay (DiaSorin, Saluggia, Italy), with a cutoff of < 33.8 BAU/ml as a positive test result. As per instruction for users [5], a cutoff of 520 BAU/ml (which has 85% positive predictive value for a microneutralization antibody titer ≥ 1:80) was chosen to stratify patients.

Anti-Receptor Binding Domain (RBD) NAb in serum was assessed by competitive ELISA in 38 HCWs, following the manufacturer's instructions (cPASS^{TM} SARS-CoV-2 Neutralization Antibody Detection Kit, GenScript). The optical density (OD) average of the negative controls was used to calculate the percentage of inhibition according to the formula: (1 – OD value of the sample / OD value of negative control) x 100%. A cut-off value of 30% was used to discriminate between the presence or absence of NAb, according to the manufacturer's instructions. In case of positivity, the percentage of inhibitory activity (INH) was also assessed.

The clinical protocol for sample and data collection and the informed consent were approved by the Institutional Ethics Committee (Comitato Etico dell'Insubria, no. 165/2020).

Abbreviations: HCW, healthcare workers; NPS, nasopharyngeal swab; VBT, vaccine breakthrough.

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Table 1
Baseline demographic and laboratory characteristics of the 64 subjects enrolled in the study

Parameter	BNT162b2	BNT162b2 plus quadrivalent flu vaccine
No. examined	28	36
Female / Male	20 / 8	20 / 16
Age (mean years ± standard deviation)	44 ± 11	43 ± 11
No with past-COVID disease (%)	4 (14)	7 (19)
Median BAU/ml of anti-S Ab pre-3rd dose (95% CI)	207 (194 – 506)	217 (207 – 499)
Median %INH of AntiRBD Nab pre-3rd dose (95% CI)	61,9 (54,6-69,2)	63,9(56,35-71,4)

BAU, binding arbitrary unit
% INH, percentage of inhibitory activity (n=38)
95% CI, 95% confidence limit

Table 2
Safety and efficacy of interventions, according to baseline anti-S1/S2 IgG level

Parameter	No.	BNT162b2	No.	BNT162b2 plus quadrivalent flu vaccine
No. with adverse effects (%)	28	20 (71)	36	18 (50)
Median anti-S Ab 14 days post-3rd dose (95% CI)				
< 520 BAU/ml	24	11400 (8929 – 14389)	30	7156 (6634 – 10755)
≥ 520 BAU/ml	4	5935 (3998 – 9118)	6	6970 (4988 – 14618)
Total	*28*	*10095 (8436 – 13424)*	*36*	*7165 (7008 – 10750)*
Median anti-S Ab Δ increase (95% CI)				
< 520 BAU/ml	24	11256 (9010 – 13880)	30	6957 (6427 – 10529)
≥ 520 BAU/ml	4	5255 (2583 – 8197)	6	6308 (4425 – 13111)
Total	*28*	*9475 (8050 – 13110)*	*36*	*6773 (6694 – 10358)*
Median %INH of AntiRBD Nab post-3rd dose (95% CI)	19	90,3(89,9-90.7)	19	90,2(-89,8-90,6)

BAU, binding arbitrary unit
% INH, percentage of inhibitory activity
95% CI, 95% confidence limit

Results

Table 1 shows the demographic and serological characteristics of participants at baseline, while Table 2 shows the results (increases from baseline) according to the anti-S1/S2 IgG starting level before vaccination. Despite the indication for the third BNT162b2 dose was blinded, 16% of HCW had baseline values that predicted low neutralizing antibody levels. No statistically significant differences were found between the two entire cohorts or sub-cohorts.

Discussion

Influenzavirus, after its disappearance during the COVID19 pandemic, is now resurfacing thanks to tapering of social isolation measures [6], and flu vaccine campaigns need to be rapidly implemented to prevent recrudescence of mortality. Preliminary *in vitro* evidence suggest that co-infection of influenzavirus A aggravates SARS-CoV-2 infection and disease severity [7].

This study has several limitations, including the small sample size, the lack of randomization, and lack of determination of anti-influenza antibody responses. Our preliminary findings nevertheless show that concomitant vaccination has no detrimental impact on safety or immune responses.

While several manufacturers are developing combined (same-syringe) vaccines, synchronous but different-syringe vaccination seems a safe and effective approach to increase compliance while preserving efficacy.

Declaration of Competing Interest

We declare we have no conflict of interest related to this manuscript.

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