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Short communication

Immunogenicity and reactogenicity of BNT162b2 booster in BBIBP-CorV-vaccinated individuals compared with homologous BNT162b2 vaccination: Results of a pilot prospective cohort study from Lebanon

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ABSTRACT

Facing new COVID-19 waves, the effectiveness of BBIBP-CorV has been noted to be low in countries whose populations were already administered two doses of the vaccine. Heterologous vaccination using ChAdOx1-S/BNT162b2 elicited higher immunogenicity compared with homologous immunization. BBIBP-CorV/BNT162b2 combination is worth testing. In this pilot prospective cohort study conducted at Makassed General Hospital, Beirut, Lebanon, from February 17, 2021, to June 30, 2021, we tested the safety and immunogenicity of a BNT162b2 booster dose in COVID-19-naïve individuals who had received two doses of the BBIBP-CorV vaccine. Heterologous booster vaccination was found to be safe and well tolerated. It was significantly associated with higher anti-spike IgG geometric mean titers compared to that after homologous BNT162b2 immunization in COVID-19-naïve individuals [(8040 BAU/mL, 95% confidence interval (CI), 4612–14 016) vs (1384 BAU/mL, 95% CI, 1063–1801), respectively, (P < 0.0001)]. In countries with limited access to mRNA vaccines and where populations have already received BBIBP-CorV, mixing BBIBP-CorV/BNT162b2 is seen to overcome the low immunogenicity induced by BBIBP-CorV alone, thus potentially providing protection against emerging variants.

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1. Introduction

The eradication of smallpox has shown that active immunization is the most important strategic approach in the fight against infectious diseases [1]. Since the beginning of the COVID-19 pandemic, researchers and public health officials have been actively working to produce and deliver COVID-19 vaccines [2]. No single vaccine can respond alone to the global demand, and no single vaccine can achieve eradication or even control of the pandemic [2]. Thus, every means of prevention should be used, and all its potentials should be exploited. So far, Pfizer-BioNTech’s mRNA COVID-19 vaccine (BNT162b2) has been granted United States Food and Drug Administration (FDA) approval for use in subjects aged above 18 years [3]. Other vaccines, including Moderna’s mRNA vaccine, Johnson & Johnson’s adenovirus vector vaccine, and Oxford–Astra Zeneca’s adenovirus vector vaccine (ChAdOx1-S), have been granted emergency use authorization (EUA) by the FDA and the European Medicines Agency (EMA) [2]. Few others have been granted EUA in the countries of production and have been used in countries where FDA or EMA authorizations are not mandatory, such as China’s Sinovac and Sinopharm vaccines and Gamaleya’s Sputnik V vaccine [2].

Based on real-life data, it can be noted that the effectiveness of the Chinese Sinopharm vaccine (BBIBP-CorV) is low in countries like Mongolia, Seychelles, and Bahrain, which lately have been facing new COVID-19 waves of infection despite their populations already administered with two doses of the vaccine [4]. In late 2020, other countries like the United Arab Emirates (UAE) released results of an interim analysis conducted by the China National Biotec Group (a subsidiary of Sinopharm) of the vaccine’s phase 3 tri-
als in Abu Dhabi, which found that the vaccine was 86% effective [5]. During the same period, China announced that BBIBP-CorV effectiveness had reached 79% based on its own interim trial data, without releasing phase 3 results, which conflicted with the UAE findings [5]. Accordingly, the UAE Ministry of Health started offering a booster dose after full vaccination with BBIBP-CorV [5]. This booster was either a third BBIBP-CorV dose or a BNT162b2 dose, and so far, there are no published data about the immunogenicity or safety of such protocols.

In April 2021, a “mix and match,” multicenter, open-label, randomized, controlled phase 2 trial (CombiVacS) was undertaken in Europe [6]. This trial has investigated the immunogenicity and reactogenicity of a BNT162b2 booster in ChAdOx1-S-primed participants after the appearance of rare, but severe, thrombotic events with thrombocytopenia in young people vaccinated with ChAdOx1-S [6]. This heterologous vaccination was proven to be safe and triggered a higher immune response than homologous counterpart vaccination [6]. The acceptable immunogenicity and safety profile achieved by heterologous vaccination involving ChAdOx1-S/BNT162b2 paved the way for other potential vaccine combinations [6]. In view of the low effectiveness of BBIBP-CorV vaccination and the apparent permissiveness in the vaccination mixing strategy, it would have been interesting to establish whether giving individuals vaccinated with two BBIBP-CorV doses a single BNT162b2 dose is safe and whether it boosts the immune response to a level that can match more effective vaccine regimens. A “mix and match” combination including BBIBP-CorV/BNT162b2, if successful in inducing an acceptable immunogenicity and safety, would provide vaccination programs in several countries with the needed flexibility in times where vaccine demand may exceed supplies.

In this study, we have primarily assessed whether boosting COVID-19-naïve individuals who previously received two BBIBP-CorV doses with a single dose of BNT162b2 is safe, and whether it can trigger humoral immunity comparable to that induced by standard homologous immunization with two BNT162b2 doses. Further, we aimed to compare humoral immunity induced by a single dose of BNT162b2 in individuals with previous COVID-19 to that produced by two BNT162b2 doses in COVID-19-naïve individuals.

2. Materials and methods

2.1. Study design and participants

This is a pilot prospective cohort clinical study conducted at Makassed General Hospital, Beirut, Lebanon, from February 17, 2021 to June 30, 2021. Participants were labeled as COVID-19-naïve or with previous documented COVID-19 infection based on their clinical history taken upon presentation to the vaccination clinic. Individuals had to report whether they had had a documented COVID-19 infection or any febrile illness since the beginning of the pandemic. If they had had a previous, documented COVID-19 infection and recovered from it, they were included in the group of previously infected individuals. Subjects were excluded if they previously had a non-investigated/non-diagnosed febrile illness since the beginning of the pandemic.

This study included three groups of participants of both genders, 18 years of age or older.

1. Group 1 (BNT162b2 group; COVID-19 naïve): received BNT162b2/BNT162b2 (21 days apart), had no history of COVID-19 when interviewed at presentation to the vaccination clinic, and did not previously receive any other type of COVID-19 vaccine.

2. Group 2 (BNT162b2 group; with history of COVID-19): received BNT162b2/BNT162b2 (21 days apart), had proven COVID-19 infection and recovery before presentation, and did not previously receive any other type of COVID-19 vaccine.

3. Group 3 (BNT162b2 booster group): had received two BBIBP-CorV doses within the preceding 3 months with no history of COVID-19 infection or any non-investigated/non-diagnosed febrile illness since the beginning of the pandemic, and were willing to receive a single BNT162b2 dose upon referral to our center by their treating physicians.

Among the three groups, included subjects were in good health and had stable clinical pictures. All were immunocompetent and did not have any known or suspected allergy or history of anaphylaxis or other serious adverse reactions to BNT162b2 vaccine excipients or any contraindication to the administration of the BNT162b2 vaccine.

The participant ratio in Groups 1, 2 and 3 was 1:0.5:1, respectively. In Group 2, due to the limited number of available immunoassay test kits, we did a digital random selection of 25 individuals from the original pool of individuals who already experienced COVID-19 before vaccination and who met the study inclusion criteria. In Group 3, we included all individuals who presented to our center and who matched the formerly mentioned inclusion criteria (N = 50). Accordingly, we matched these individuals for age and gender in Group 1 only (N = 50).

Ethics approval was obtained from our facility’s Institutional Clinical Research Ethics Committee (approval number: 1522021). All participants signed a voluntary Informed Consent Form for screening evaluation, providing demographic and clinical data and participation consent.

2.2. Sample collection and assessment of immunogenicity

Sequential blood samples were collected from participants in Groups 1 and 2 to determine titers of anti-spike immunoglobulin G (anti-S-IgG) measured by immunoassay on two occasions (21 days after the first dose and 14 days after the second dose). In Group 3, blood samples were collected from participants at presentation for the receipt of the booster dose and then 14 days after it.

Sample analysis was run at the microbiology laboratory of our hospital. Antigen–specific humoral immune response was analyzed using the Elecsys Anti-SARS-CoV-2 S assay (Roche Diagnostics, Mannheim, Germany), which is an electrochemiluminescence immunoassay used to detect antibodies (including IgG) to the SARS-CoV-2 spike protein receptor-binding domain on the Cobas-e601 immunoassay analyzer (Roche Diagnostics, Basel, Switzerland) [7].

2.3. Safety of BNT162b2 booster dose in Group 3

Safety data consisted of solicited local and systemic adverse events (AE) collected on days 3 and 14 after booster vaccination in participants of Group 3, through telephone interviews according to a prepared checklist [8].

Patient follow-up

Participants in the 3 groups were followed up on a monthly basis by telephone interviews regarding the occurrence of any febrile or flulike illness or documented COVID-19 after vaccination.

2.4. Statistical analysis

Categorical analyses on gender and age, presented as number and percentage, were performed using chi-square test. Antibody
titers [anti-S-IgG measured in binding-antibody units (BAU)/mL] were presented as geometric mean (GM) and 95% confidence interval (CI) or median and interquartile range (IQR), unless otherwise stated. The one-sample Kolmogorov–Smirnov test was used to check for normality of the data distribution. The Kruskall–Wallis test, followed by Dunn’s multiple comparison post hoc test, was performed to compare unpaired non-parametric data between the groups (antibody levels). Differences between groups were considered to be significant at a p-value of < 0.05. Analysis was carried out using the IBM Statistical Package for the Social Sciences program for Windows (version 23.0) (Armonk, NY, USA:IBM Corp.) and GraphPad Prism 9.0 software (GraphPad Software, Inc., San Diego, CA, USA) using two-tailed tests.

3. Results

The pilot study profile is illustrated in Fig. 1. In total, 125 individuals agreed to participate and met the inclusion criteria: 50

![Fig. 1. Pilot study profile.](image)
In Group 3, the median time elapsed since the second BBIBP-CorV dose and the BNT162b2 booster dose administration was 63 days (IQR, 45–93 days).

As regards safety, BNT162b2 booster vaccination was found to be safe and well tolerated. Out of the 50 participants, 31 (62%) experienced more than one mild-to-moderate AE: generally, pain at the site of injection (60%) and lethargy (10%). Participants who experienced these adverse event were mostly aged between 18 and 54 years (20/31, 64.5%) [Table 2]. There was no evidence of thrombotic events or bleeding and no other potentially life-threatening reactions reported within 14 days of vaccination. There were no hospitalizations due to solicited symptoms.

Results of anti-S-IgG titers (log transformed) in the three groups are presented in Table 3 and Fig. 2. A statistically significant difference was noted between groups as determined via Kruskal–Wallis test [Table 1].

In Group 1, 43 of the 50 participants (86%) were humorally reactive to the first BNT162b2 dose, with an anti-S-IgG GM titer (GMT) of 17 BAU/mL (95% CI, 10–27). After the second dose, all participants were humorally reactive, with the anti-S-IgG GMT significantly increasing to 1384 BAU/mL (95% CI, 1063–1801) (P < 0.0001) [Fig. 2].

In Group 2, all of the COVID-19-recovered participants were humorally reactive to the first BNT162b2 dose, with an anti-S-IgG GMT of 6798 BAU/mL (95% CI, 2675–17 277), and this value was observed to significantly increase after the second dose (22 536 BAU/mL, 95% CI, 13 550–37 482) (P = 0.04) [Fig. 2].

In Group 3, 40 of the 50 (80%) participants were humorally reactive after two doses of BBIBP-CorV, with an anti-S-IgG GMT of 9 BAU/mL (95% CI, 6–13). Two weeks following boost immunization with BNT162b2, all participants were reactive, with the anti-S-IgG GMT significantly increasing to 8040 BAU/mL (95% CI, 4612–14 016) (P < 0.0001) [Fig. 2].

In our study, we found that anti-S-IgG GMT levels after the first BNT162b2 dose in COVID-19-naïve cases was almost similar to the immune response in individuals who received booster immunization with BNT162b2 in Group 3 (P = 0.99) [Fig. 2].

In Groups 1 and 2, none of the participants developed COVID-19 infection anytime after vaccination. In Group 3, 2 participants out of 50 (4%) developed COVID-19 (positive SARS-CoV-2 RNA RT-PCR) one week after the administration of the BNT162b2 booster dose. One was asymptomatic and the other had mild symptoms for 5 days with no need for supplemental oxygen or hospitalization. Subsequently, the asymptomatic case had a negative RT-PCR test one week after the first positive test. The second case tested negative 13 days after the first positive RT-PCR test.

4. Discussion

As per our findings, it was determined that the heterologous BBIBP-CorVx2/BNT162b2 booster immunization regimen was well tolerated, with pain or tenderness at the site of injection as the most common AE documented in 60% of the recipients, generally in the 18–54 years age group. These findings mirrored the reactogenicity pattern reported by BNT162b2 pivotal trials and systematic reviews on COVID-19 vaccine safety indicating a low incidence of AE and a safety profile characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache [9–11].

In a randomized, double-blind, placebo-controlled phase 1/2 trial at Shangqiu City Liangyuan District Center for Disease Control and Prevention in Henan Province, China, Xia et al. showed that anti-spike and neutralizing antibody levels followed parallel patterns after the receipt of two BBIBP-CorV doses [11,12]. More recently, Earle et al. showed a positive robust correlation between binding-antibody titer post-vaccination and efficacy (Spearman's rank correlation coefficient = 0.93) and between neutralizing titer and efficacy (Spearman's rank correlation coefficient = 0.79) [13]. These findings mean that higher anti-spike and neutralizing antibody titers correlated with higher vaccine efficacy, despite uncontrolled variables across the clinical trials including the geographically diverse populations subject to different circulating wild-type SARS-CoV-2 and its variants; the use of different clinical endpoints; differing available serological assays; differing convalescent sera panels; and different manufacturing platforms [13].

In our study, we found that anti-S-IgG GMT levels after the first BNT162b2 dose in COVID-19-naïve cases were almost comparable to those in participants who received two doses of BBIBP-CorV. On the other hand, in the pivotal BNT162b2 trial, Polack et al. reported an efficacy of 52% (95% CI, 29.5–68.4) between the first dose and the second dose, and a similar effectiveness has been reported by countries that have used inactivated SARS-CoV-2 virus vaccines (e.g., BBIBP-CorV), such as Chile, Mongolia, Bahrain, and the UAE.
It is worth noting that homologous BNT162b2 vaccination resulted in an efficacy rate of 94.6% (95% CI, 89.9–97.3) in pivotal clinical trials [11,15].

Our data have also shown that humoral immunity induced by the BNT162b2 booster in individuals immunized with two BBIBP-CorV doses was significantly higher than that produced by two BNT162b2 doses in COVID-19-naive cases. Based on this information, boosting the anti-spike IgG titer would eventually boost the efficacy and effectiveness levels of this sequential vaccination, aiming to be non-inferior to that triggered by homologous BNT162b2 vaccination. It is important to maintain adequate IgG levels to protect vaccinated individuals against wild-type SARS-CoV-2 but also its emerging resistant variants, which are demonstrating certain immunity escape [2,16]. Furthermore, a significant robust correla-

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**Fig. 2.** Immune responses against the SARS-CoV-2 spike protein after vaccination with homologous (BNT162b2/BNT162b2) and heterologous sequential (BBIBP-CorVx2/BNT162b2) regimens.
tion was documented between the Elecsys anti-spike assay from Roche Diagnostics and a surrogate virus neutralization assay (correlation coefficient $> 0.86$, $P < 0.001$) [17].

Regarding the two cases that developed COVID-19 after the booster BNT162b2 in the individuals previously immunized with two BBIBP-CorV doses, we cannot consider them as breakthrough infections since both occurred one week following the booster dose. The United States Centers for Disease Control and Prevention (CDC) defines a vaccine breakthrough infection as the detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected from an individual 14 days or more after he has completed the full-recommended doses of an FDA-authorized COVID-19 vaccine [18]. This can be attributed to the low efficacy achieved by inactivated SARS-CoV-2 virus vaccines, as previously mentioned [4,5,9,11,14].

Mixing different types of COVID-19 vaccines has been reported in certain European countries, such as France and Germany, for people who received a first dose of ChAdOx1-S but are from young age groups for which vaccine was no longer recommended by health authorities in these countries due to the development of severe thrombotic events with thrombocytopenia [6,19,20]. This practice has been discouraged by the World Health Organization who said that there is currently no solid data on vaccine interchangeability [21].

Our findings may help find a potential solution for countries that have immunized their populations with BBIBP-CorV and are now suffering from new COVID-19 waves of infection. Giving a single BNT162b2 booster dose to their vaccinated population may increase herd immunity levels within 15 days. In addition, a widespread policy of mixing different vaccines could also help make COVID-19 vaccination programs flexible with regard to variations in supply and procurement, especially in countries with specific vaccine shortage or limited accessibility and even in settings where multiple vaccines might be available in relatively small quantities. In such cases, this practice can stretch the benefit from a specific type of vaccine and can revive other vaccines that could be available, but alone did not prove to ensure the desired effectiveness.

Our study has its limitations, as it is not a randomized controlled trial and has a small sample size. The time elapsed since the second BBIBP-CorV dose administration and the BNT162b2 booster dose administration was not standardized. Cellular immunity was not checked, and anti-S-IgG was only the surrogate marker of neutralizing antibodies. This is a sequential vaccination study, yet for a “mix and match” one, it is worth testing one BBIBP-CorV dose followed by one BNT162b2 dose. In addition, efficacy and effectiveness studies are to follow.

5. Conclusion

This pilot study provides evidence that heterologous BBIBP-CorVx2/BNT162b2 immunization is safe and significantly more immunogenic than homologous BNT162b2 vaccination. Sequential vaccination can be a solution to countries that have already been given BBIBP-CorV and are now struggling with outbreaks. This practice triggers a strong and robust immunogenic response that may potentially protect against emerging variants. This can help overcome procurement obstacles of specific vaccines, where no single vaccine alone can respond to the global demand.

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.

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Author Contributions

Rima Moghnieh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dania Abdallah, Rana Mekdashi and Salam El-Hassan contributed equally to the study. Mohamed H Sayegh and Abdul Rahman Bizri equally shared senior co-authorship. All authors read and approved the final version of the manuscript.

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