Immunogenicity of BNT162b2 and CoronaVac boosters in fully vaccinated individuals with CoronaVac against SARS-CoV-2: A Longitudinal Study

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January 16, 2022

Abstract

Objective: There is a need for the immunogenicity of different boosters after widely used inactivated vaccine regimens. We aimed to determine the effects of BNT162b2 and CoronaVac boosters on the humoral and cellular immunity of individuals who had two doses of CoronaVac vaccination. Methods: The study was conducted in three centers (Koc University Hospital, Istanbul University Cerrahpasa Hospital, and Istanbul University, Istanbul Medical School Hospital) in Istanbul. Individuals who had two doses of CoronaVac and no history of COVID-19 were included. The baseline blood samples were collected three to five months after two doses of CoronaVac. Follow-up samples were taken one and three months after third doses of CoronaVac or one dose of mRNA BNT162b2 boosters. Neutralizing antibody titers were detected by plaque reduction assay. T cell responses were evaluated by Elispot assay and flow cytometry. Results: We found a 3.38-fold increase in neutralizing antibody titers (Geometric Mean Titer [GMT], 78.69) one month after BNT162b2 booster and maintained at the three months (GMT, 80). However, in the CoronaVac group, significantly lower GMTs than BNT162b2 after 1 month and 3 months (21.44 and 28.44, respectively) indicated the weak immunogenicity of the CoronaVac booster ($p<0.001$). In the ELISpot assay, IL-2 levels after BNT162b2 were higher than baseline and CoronaVac booster ($p<0.001$) and IFN-γ levels were significantly higher than baseline ($P<0.001$). The CD8+CD38+CD69+ and CD4+CD38+CD69+ T cells were stimulated significantly at the 3 rd month of the BNT162b2 boosters. Conclusion: The neutralizing antibody levels after three months of the BNT162b2 booster were higher than the antibody levels after CoronaVac. On the other hand, specific T cells might contribute to immune protection. By considering the waning immunity, we suggest a new booster dose with BNT162b2 for the countries that already have two doses of primary CoronaVac regimens.

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Highlights

* Neutralizing antibody response is higher with BNT162b2 than CoronaVac boosters in one month and three months after vaccination.

* T cell activation is significantly higher with BNT162b2 than CoronaVac boosters one month after vaccination

* The ratio of CD8+CD38+D69+ effector cells is higher than baseline after BNT162b2 booster in three months

Summary

Objective: There is a need for the immunogenicity of different boosters after widely used inactivated vaccine regimens. We aimed to determine the effects of BNT162b2 and CoronaVac boosters on the humoral and cellular immunity of individuals who had two doses of CoronaVac vaccination.

Methods: The study was conducted in three centers (Koc University Hospital, Istanbul University Cerrahpasa Hospital, and Istanbul University, Istanbul Medical School Hospital) in Istanbul. Individuals who had two doses of CoronaVac and no history of COVID-19 were included. The baseline blood samples were collected three to five months after two doses of CoronaVac. Follow-up samples were taken one and three months after third doses of CoronaVac or one dose of mRNA BNT162b2 boosters. Neutralizing antibody titers were detected by plaque reduction assay. T cell responses were evaluated by Elispot assay and flow cytometry.

Results: We found a 3.38-fold increase in neutralizing antibody titers (Geometric Mean Titer [GMT], 78.69) one month after BNT162b2 booster and maintained at the three months (GMT, 80). However, in the CoronaVac group, significantly lower GMTs than BNT162b2 after 1 month and 3 months (21.44 and 28.44, respectively) indicated the weak immunogenicity of the CoronaVac booster ($p<0.001$). In the ELISpot assay, IL-2 levels after BNT162b2 were higher than baseline and CoronaVac booster ($p<0.001$) and IFN-γ levels were significantly higher than baseline ($P<0.001$). The CD8+CD38+CD69+ and CD4+CD38+CD69+ T cells were stimulated significantly at the 3rd month of the BNT162b2 boosters.

Conclusion: The neutralizing antibody levels after three months of the BNT162b2 booster were higher than the antibody levels after CoronaVac. On the other hand, specific T cells might contribute to immune protection. By considering the waning immunity, we suggest a new booster dose with BNT162b2 for the countries that already have two doses of primary CoronaVac regimens.

Introduction

The worldwide use of effective and safe COVID-19 vaccines is still of high priority to control the pandemic and to reduce the burden of COVID-19. The vaccine type and vaccination schedule affect many of the cellular and molecular elements of innate and adaptive immune systems. Estimating the immune responses after SARS-CoV-2 vaccinations is one of the important parameters to make predictions of the pandemic and the need for the booster vaccine doses. Therefore, testing the effectiveness of COVID-19 vaccines in

different vaccination schedules is necessary, but there are a variety of vaccines and their schedules based on the availability of the vaccines in the global supply. Following primary vaccination, antibody and T cell responses have been decreased over time[1]. A booster dose six months after the second dose of various vaccines significantly increased neutralizing antibody concentrations[2]. The heterologous vaccine regimens were reported to stimulate neutralizing antibodies more than the homologous vaccine protocols[3].

In Turkey, the inactivated vaccine CoronaVac (Sinovac Life Sciences, Beijing, China) was the first one that was approved by the Ministry of Health. Healthcare workers and individuals over 65 years of age were suggested two doses of CoronaVac administered two months apart in the initial phase of the vaccination program[4]. After about six months, the Ministry of Health of Turkey recommended a booster of mRNA vaccine (BNT162b2) as an alternative option to the CoronaVac booster. In early studies of the CoronaVac, effectiveness after two-dose schedules was reported as 60-90% [4,5]. Nevertheless, these studies were performed approximately 6 weeks after the second dose. After six months of the second dose of CoronaVac, neutralizing antibody titers declined below the seropositivity cut-off but a remarkable increase in the neutralizing antibody concentrations was observed with administration of a third dose [6]. However, knowledge of the humoral and cellular immune responses elicited by BNT162b2 and CoronaVac boosters following two doses of primary CoronVac vaccination is still limited. In this study, we aimed to explore the neutralizing antibody and T cell responses after the booster doses of CoronaVac and BNT162b2 following two doses of CoronaVac.

Materials & Methods

Study Design and Participants

The study was conducted in three centers (Koç University Hospital, Istanbul University Cerrahpasa Hospital, and Istanbul University, Istanbul Medical School Hospital) in Istanbul. Individuals who had two doses of CoronaVac and no history of COVID-19 were included in the study. The baseline blood samples were collected three to five months after 2 doses of CoronaVac. Follow-up samples were taken one and three months after the third dose of CoronaVac or one dose of the mRNA BNT162b2 vaccine (Figure 1). All the individuals were followed up for SARS-CoV-2 infection. Sampling was approved by The Institutional Review Board of Koç University with the number of 2021. 151.IRB1.055.

A total of 52 individuals received two doses of CoronaVac and whole blood samples were collected 3-5 months after vaccination. (n= 19 for 3 months, n=26 for 4 months, n=7 for 5 months.) One month after receiving the 3rd dose (booster) vaccine, whole blood samples were collected from the same 52 individuals. (n=42 for BNT162b2 and n=10 for CoronaVac) . Because of changed vaccine recommendations due to variant of concerns, some volunteers received the 4th dose of BNT162b2 or CoronaVac vaccine, therefore excluded from the study. Therefore, six participants from the BNT162b2 booster group and four participants from the CoronaVac booster group donated blood samples 3 months after the booster dose.

Immunological Assays

Humoral and cellular immune responses were examined to compare the serum SARS-CoV-2 neutralizing antibody concentrations and T cell reactivity in peripheral blood mononuclear cells (PBMC).

PBMC Isolation

Whole blood was collected from the donor and PBMC was isolated by Ficoll density gradient centrifugation method [7] and stored in the -80°C [8].

Flow Cytometry for T cell response

For T cell assays, 2 x 106 PBMCs were seeded in RPMI 1640 media supplemented with 5% AB serum for each of the 96 well plates. T cells were activated by using a SARS-CoV-2 Spike protein-specific peptivator and were incubated for 20 hours at 37°C 5% CO2 incubator. T cells were stained with a viability dye and T cell surface markers antibodies (CD3-FITC, CD4-PerCP-Cy5.5, CD8-Brilliant Violet 510, CD38- PE-Cy7, CD69-APC, Brilliant Violet 605, CD14-APC-Cy7, CD19-APC-Cy7) (Biolegend). PMA/Ionomycin, CMV, and DMSO were used as controls. Samples were run by Attune Flow cytometer.

Plaque reduction neutralization test (PRNT50)

A live SARS-CoV-2 Wuhan strain (B303) which was previously isolated from the SARS-CoV-2 RdRp PCR positive nasopharyngeal specimen (The GenBank accession number MT675956) was used for the plaque assay. TCID50/ml of the SARS-CoV-2 used for plaque assay was 2x106. Vero E6 cells (ATCC CRL-1586) were cultured with DMEM High-Glucose (Gibco, 41966-029) supplemented with 10% Fetal bovine serum (FBS),(Gibco, 10500064), 1% Penicillin-Streptomycin and Amphotericin B (Sigma, A2942). The serum of each donor was incubated with SARS-CoV-2 at the multiplicity of infection (MOI) 0.01 for 1 hour at 37°C, 5% CO2, and then inoculated onto the VeroE6 cells at 100% confluency. After incubation for 1 hour at 37°C, 5% CO2, the serum-virus mixture was discarded. The cell monolayers were coated with 2% methylcellulose and 5% Fetal bovine serum (FBS)/ DMEM mixture (1:1). Four days after infection, methylcellulose and DMEM mixture was discarded. Plates were washed and cells were fixed with 4% PFA then stained with crystal violet. Plaques were counted with the naked eye and the Celigo Image cytometer (Nexcelom, Celigo Image Cytometer 200-BFFL-5C). The virus control was studied in duplicate in each assay. A negative control (unexposed unvaccinated individuals' serum samples) and an assay control were included in each study [9].

Elispot Assay for T cell response

The IFNγ and IL-2 responses of T cells were studied with Fluorospot Assay (Abcam Fluorospot, USA) according to the manufacturer's instructions. Thus, plates were incubated for 30 seconds at room temperature with 35% ethanol and washed with DPBS 1X. The capture antibodies were added and incubated overnight at +4°C. After washing with DPBS 1X, RPMI containing 10% FBS cell culture media was added into the wells and incubated for 2 hours at room temperature. Plates were washed with DPBS 1X and 100.000 cell suspension was added into each well with appropriate concentration of SARS-CoV-2 S peptide activator (PepTivator®SARS-CoV-2 Prot S-research grade (6nmol/peptide, Miltenyi Biotec, Germany). Cells were incubated at 37°C in a CO2 incubator for 20 hours and were washed 3 times. Detection antibodies were added and incubated for 1 hour 30 minutes at RT. After washing, FITC-green fluorescence conjugate/Streptavidin-phycoerythrin solution (for IFNγ/IL-2 respectively) was added to each well and incubated for 1 hour at RT at dark. Cells were washed three times again and all residuals buffer was removed with distilled water. After drying, spots were read with GFP and RFP filters, Leica M205 FA under a dissection microscope. The PMA/Ionomycin was used as a positive control, DMSO was used as a negative control, CMV virus was used for cross-reaction, and tests were performed in duplicate.

Statistical Analysis

The statistical analysis was performed by using a non-parametric test (Mann Whitney U) for the comparison of two different groups by using STATA (16v, USA). For the analysis and visualization of the obtained data GraphPad Prism 8.0.2 Software is used.

Results

The demographic characteristics of the participants were presented in table 1. Both vaccine boosters produced detectable PRNT50 antibody titers (Figure 2A). Three to five months after two doses of CoronaVac, 40 of 52 (76.92%) participants had neutralizing antibodies above 1/20 with a GMT of 23.27 (range between <1:10 to 1:80). One month after administration, BNT162b2 booster induced significantly higher neutralizing antibody with GMT of 78.69 (ranging between 20 to 1280) compared to GMT of CoronaVac with 21.44 (ranging between 10 to 40; P<0.001). In this period, all participants in the BNT162b2 and 7/10 (70%) of CoronaVac receivers had PRNT50 levels >1/20 titer. The ninety-eight % of the BNT162b2 and 40% of the CoronaVac participants had antibody titers above the 1:30 threshold. In both groups, GMTs remained at similar levels at month three (Figure 2A). The neutralizing antibody levels of each participant in the study period were presented in Figure 2B.

We studied the reactivity and magnitude of CD4+ and CD8+ T cell responses to the SARS-CoV-2 spike S peptide pool. In the assessment of 33/52 patients, there was no significant change in the magnitude of CD4+ and CD8+ T cell ratios compared to baseline levels (Figure 3).

In the ELISpot assay, T cells showed significantly higher IFN-γ reactivity after BNT162b2 booster, with a median of 140 SFU per million PBMC (Range 5 SFU- 320 SFU) compared to baseline T cell response (60 SFU/106 PBMC; p<0.001). The IL-2 reactivity of the T cells, 1 month after BNT162b2 booster (60 SFU/106 PBMC) was significantly higher than CoronaVac booster (median SFU 30 /106 PBMC, p<0.05) and baseline levels (20 SFU/106 PBMC; P<0.001) (Figure 4).

We also assessed the effector T cell response after COVID-19 vaccine booster doses, by phenotyping S-specific CD4+ and CD8+ T cells. Representative gating was shown in figure S1 (supplement). One month after the BNT162b2 booster, both of the CD8+CD38+CD69+ T cells and CD4+CD38+CD69+ T cells were stimulated although not significantly compared to baseline level, however, a significant increase was detected at the 3rd month. After three months, the proportion of CD8+CD38+CD69+ T cells increased from baseline of 1.160 % to 3.130 % (p=0.031) and CD4+CD38+CD69+ T cells from 4.37 % of baseline to 10% (p=0.013). Three months after the CoronaVac booster, CD4+CD38+CD69+ T cells increased from 4.37 % of baseline to 10.20%. (Figure 5).

Discussion

The present study addresses the knowledge gap on the immunogenicity of mRNA and inactivated vaccine boosters after 2 doses of inactivated CoronaVac administration. We focused on neutralizing antibody and T cell responses after one and three months elicited by BNT162b2 (mRNA) and CoronaVac (inactivated) vaccine boosters in fully vaccinated individuals with CoronaVac.

We found a 3.38-fold increase in neutralizing antibody titers (GMT 78.69) one month after the BNT162b2 booster and antibody titers were found to be maintained after three months (GMT 80). However, in the CoronaVac group, low GMTs after 1 month and 3 months (21.44 and 28.44) indicated the weak immunogenicity of the CoronaVac booster. For the protection of 50% of the individuals, a neutralizing antibody titer of 1:19 for BNT162b2 and 1:30 for CoronaVac was suggested as cutoff levels of protection [10]. All BNT162b2 booster receivers had antibody levels above the protection threshold of 1:19 after three months, but only 40% of donors had antibody titers above the 1:30 threshold in the CoronaVac group. High neutralizing antibody levels following 14 days after CoronaVac booster dose [11] and decreased neutralizing antibody levels 28 days after the CoronaVac booster was reported [12]. We found low neutralizing antibody levels at a prolonged time (1 to 3 months) after booster doses of CoronaVac. The concern about the weak immunogenicity would be increased by considering the reduced efficacy of vaccines against the omicron variant [13,14].

Current vaccine trials have focused on the stimulation of the neutralizing antibody against SARS-CoV-2, but CD4+ and CD8+ cells also might provide protection from severe disease and support resolution of COVID-19 [15]. In our cohort, the magnitude of post BNT162b2 booster responses was higher than the CoronaVac booster. We detected increased IFNγ and IL-2 reactivity after the BNT162b2 booster, accompanied by an increase in CD8+CD38+CD69+T cells. The ratio of CD4+CD38+CD69+ cells was also high in the 3rd month of the BNT162b booster. Robust CD8 and CD4 T-cell responses to BNT162b2 were reported in clinical studies [16]. The induction of T cell responses after CoronaVac vaccination was also reported by a study from Hong Kong [17]. T cells clones against other SARS-CoV-2 antigens like N protein can also be stimulated with inactivated vaccines[18]. The type of peptide pool used for activation might affect the results of T-cell response measurements [19]. In this study, we used the S-pool, rather than other peptides of the virus, which might lead to underestimation of the true magnitude of T-cell responses.

The strength of our study is being a longitudinal study and having a unique advantage of being performed in Turkey, where the primary vaccine schedule consisted of two CoronaVac doses. The study mainly has two limitations, one is related to the low sample size to detect the statistical significance especially in the CoronoVac booster group, however, the results are in parallel with reported studies that evaluated anti-S antibody titers by ELISA in Turkey[20]. Some of the recruited vaccinated donors were excluded from the study since they received 4th doses after two months. Secondly, we could not cover the newly emerged omicron variant. This will be done in future studies.

Our study has implications for the countries that used a two-dose regimen of CoronaVac. The neutralizing

antibody levels after three months of the BNT162b2 booster were higher than the antibody levels after CoronaVac. On the other hand, specific T cells might contribute to immune protection. By considering the waning immunity, we suggest a second booster dose with BNT162b2 for the countries that already have BNT162b2 or CoronaVac boosters following two doses of CoronaVac.

Acknowledgments: The authors declare no conflict of interest in relation to this work.

Author contribution: Data and sample collection: ZEK, RE, MK, YT, SSY, KM, OE

Laboratory work: ZEK, RE, GGE, TB, ZGT, YT, FC Data analysis: ZEK, RE, GGE, TB, OD, OE, FC Manuscript preparation: ZEK, RE, GGE, ZGT, OE, FC

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Figure and Table Legends:

Table 1. Baseline demographic characteristics of the participants who received the booster dose

Figure 1: The design of the study.

Figure2: Neutralizing antibody levels after BNT162b2 and CoronaVac booster doses. **A-** PRNT50 titers at baseline, one month and three months after boosters. Black lines are GMT=geometric mean titer (*P<0.001; **P<0.05). **B-** Changes in neutralizing antibody levels for each individual during a 3-month period. Dots represent neutralizing antibody titers for individuals in the population.

Figure 3. The proportion of specific T cell subpopulations after activation with SARS-CoV-2 S peptide pool. **A-**$CD4^+$ cell ratio at baseline, one month and three months after boosters. **B-** $CD8^+$ at baseline, one month and three months after boosters. Dots represent T cell ratios for individuals in the population. Black lines are median values of each population.

Figure 4. The ELISPOT results of T cells after incubation with SARS-CoV-2 S peptide pool. **A** - IFN-γ response at baseline, one month and three months after boosters. **B-** IL-2 response at baseline, one month and three months after boosters. Dots represent T cell ratios for individuals in the population, (*P<0.001; **P<0.05).

Figure 5. The ratio of $CD8^+CD38^+CD69^+$ and $CD4^+CD38^+CD69^+$cells after BNT162b2 and CoronaVac boosters. **A-**$CD8^+CD38^+CD69^+$cell ratio at baseline, one month and three months after boosters.**B-** $CD4^+CD38^+CD69^+$cell ratio at baseline, one month and three months after boosters. Dots represent T cell ratios for individuals in the population. (*P<0.05)

Supplement

S1. The gating strategy of T lymphocytes in flow cytometry.

Informed Consent: (In Turkish)

BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU

Koç Üniversitesi – İş Bankası Enfeksiyon hastalıkları Araştırma ve Uygulama Merkezi'nde Laboratuvar Prof. Dr. Füsun Can tarafından yürütülen, Koç Üniversitesi Etik Kurulları'nın 2021.151.IRB1.055. sayılı onayı ile izin verilen, **"Covid-19'a Karşı Aktif ve Pasif Bağışıklığın Hafıza Yanıtı Üzerinden Değerlendirilirmesi** " başlıklı araştırmaya katılımınız rica olunmaktadır.

Bu araştırmaya tamamen kendi iradenizle, herhangi bir zorlama veya mecburiyet olmadan gönüllü olarak katılımınız esastır. Lütfen aşağıdaki bilgileri okuyunuz ve katılmaya karar vermeden önce anlamadığınız herhangi bir husus varsa çekinmeden sorunuz.

ÇALIŞMANIN AMACI (Neden böyle bir araştırma yapmaya gerek duyuldu?)

Şiddetli akut solunum yolu sendromu koronavirüsü 2 ya da kısaca**SARS-CoV-2** , ilk kez Aralık 2019 yılında tanımlanmış Ocak 2020'de insandan insana bulaşması Dünya Sağlık Örgütü tarafından doğrulanmıştır. Şu anda bütün dünyada yüksek riskli enfeksiyon etkeni olarak kabul edilmektedir. Genel ölüm oranı 0.5% ile 3.5 % arasında değişmektedir. Ancak kimileri hastalıktan kronik olarak geçirirken kimileri asemptomatik kalmaktadır. Bu sebeple, bu enfeksiyonu geçiren hastaların uzun dönem bağışıklık hafızasının belirlenmesi oldukça önemlidir. Hafıza B, yardımcı hafıza T hücresi , sitotoksik T hücresi ve nötralizan antikorlar yeniden enfeksiyona, hastalık riskine ve aşı etkinliğine karşı korumanın belirlenmesine yardımcı olur. Fakat insanlardaki bellek türü ve SARS-CoV-2 arasındaki ilişki sınırlıdır. SARS-CoV-2' ye karşı bağışıklığı anlamak, COVID-19'a karşı koruyucu bağışıklığı anlamak ve COVID-19 pandemisinin gelecekteki olası seyrini değerlendirmek amacıyla bu çalışma planlanmaktadır.

PROSEDÜRLER

Bu çalışmaya gönüllü katılmak istemeniz halinde yürütülecek çalışmalar şöyledir. Pfizer-BioNTech aşısı yeni bir teknoloji kullanan bir haberci RNA (mRNA) aşısıdır. mRNA aşısı, vücuttaki konak hücrelere SARS CoV-2 virüsünden küçük bir genetik kod parçası iletir, ve spike proteinleri üretilip, bağışıklık yanıtı uyarılır. Bu uyarımda, virüslere bağlanarak onların etkisiz hale getirilmesini sağlayan nötralizan antikorlar oluşturulur ve hafıza hücreleri geliştirilir. CoronaVac aşısı ise, tüm virüsün bir laboratuvarda büyütülmesi ve ardından inaktive edilmesi ile geliştirilmiştir. Vücudun içine girdikten sonra, inaktive edilmiş virüsler bağışıklığı uyararak antikor ve hafıza T hücresi geliştirilmeini sağlamaktadır.

Koç Üniversitesi yürütücülüğünde çeşitli merkezlerdeki Pfizer/BionTech ya da Sinovac aşısını yaptırmış olan gönüllülerden 3., 6., 9. ve 12. aylarda 4 kez olmak üzere kan örneği alınacaktır. Alınan kan örnekleri aşı sonrası bireylerde bağışıklık hafızanın oluşup oluşmadığının araştırılması amacıyla kullanılacaktır. Kan örneklerinin bir kısmı SARS-CoV-2'ye özgü tepki gösterebilen CD4+, CD8+ ve B hafıza hücrelerinin varlığı ve miktarının değerlendirilmesi amacıyla kullanılacaktır. Kan örneklerinin kalan kısmından elde edilecek olan serum örnekleri ise SARS-CoV-2'ye özgü nötralizan antikorların varlığının ve miktarının araştırılması amacıyla kullanılacaktır. Bu incelemeler size ek bir rahatsızlık getirmeyecek ve ek bir ücret ödenmesine neden olmayacaktır. Tüm bu alınan örneklerde moleküler çalışmalar ile bağışıklık hafıza araştırılacaktır. Moleküler testler Koç Üniversitesi Mikrobiyoloji Laboratuvarında yapılacak ve yurt içi veya yurt dışında herhangi bir kuruluşa veya kişiye biyolojik materyaliniz gönderilmeyecektir.

OLASI RİSKLER VE RAHATSIZLIKLAR

Yaptığımız araştırma sizin izleminizde herhangi bir tıbbi değişikliğe neden olmayacaktır. Bu işlemler "günlük hayatta karşılaşılan risklerden daha fazla bir risk taşımamaktadır".

TOPLUMA VE/VEYA GÖNÜLLÜLERE OLASI FAYDALARI

Bu araştırma sonucunda elde edilecek bilgiler SARS-CoV-2 enfeksiyonlarından etkin korunma sağlanmasında ve hastalığın yayılmasının önlenmesinde toplumun geneline olumlu katkısı sağlayacaktır. Önlenebilen her enfeksiyonun ülke ekonomisine katkısı açıktır.

GİZLİLİK

Tüm kişisel bilgileriniz 24.03.2016 'da Türkiye Büyük Millet Meclisi'nde kabul edilmiş ve 07.04.2016 tarihli ve 29677 sayılı Resmi Gazete'de yayımlanarak yürürlüğe girmiş olan Kişisel Verilerin Korunması Kanunu (KVKK) ve ilgili mevzuat hükümleri gereğince sadece araştırmaya katılan kişilerin ulaşabildiği şifre korumalı internet tabanlı bir programda saklanacak, bilgileriniz sadece bu araştırma için kullanılacak ve yasal süre sona erdiğinde silinecek/imha edilecektir. Bu çalışmayla bağlantılı olarak elde edilen ve sizinle özdeşleşmiş her bilgi gizli kalacak, 3. kişilerle paylaşılmayacak ve yalnızca sizin izniniz ile ifşa edilecektir. Araştırmacılar,

denetleyiciler, etik kurul üyeleri, kurum ve diğer ilgili sağlık otoriteleri sizin tıbbi kayıtlarınıza doğrudan erişimde bulunabilir, ancak bu bilgiler gizli tutulmak zorundadır. Bu formu imzalanmasıyla adı geçen kişilere erişime izin vermiş olacaksınız.

KATILIM VE AYRILMA

Bu çalışmanın içinde olmak isteyip istemediğinize tamamen kendi iradenizle ve etki altında kalmadan karar vermeniz önemlidir. Katılmaya karar verdikten sonra, herhangi bir anda sahip olduğunuz herhangi bir hakkı kaybetmeden veya herhangi bir yaptırıma maruz kalmadan istediğiniz zaman ayrılabilirsiniz.

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Yukarıda yapılan açıklamaları anladım. Sorularım tatmin olacağım şekilde yanıtlandı. Söz konusu araştırmaya, hiçbir baskı ve zorlama olmaksızın kendi rızamla katılmayı kabul ediyorum. Dilediğim zaman ayrılma hakkım saklı kalmak koşulu ile bu çalışmaya katılmayı onaylıyorum. Bu formun bir kopyası da bana verildi.

Katılımcı Adı-Soyadı

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Katılımcı İmzası Tarih

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Araştırmacının İmzası Tarih

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`Figures .docx` available at https://authorea.com/users/455648/articles/552940-immunogenicity-of-bnt162b2-and-coronavac-boosters-in-fully-vaccinated-individuals-with-coronavac-against-sars-cov-2-a-longitudinal-study

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`Table 1.docx` available at https://authorea.com/users/455648/articles/552940-immunogenicity-of-bnt162b2-and-coronavac-boosters-in-fully-vaccinated-individuals-with-coronavac-against-sars-cov-2-a-longitudinal-study