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# Mixing and Matching COVID-19 Vaccination for Countries of COVID-19 Vaccine Shortage

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## *Abstract*

*A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including ScienDirect, PubMed, Scopus, and ISI Web of Science. The search was applied to the articles that were published between January 2021 and September 2021. With strict literature search and screening processes, it yielded 8 articles from 106 articles of initial literature database. In June 2021, a preliminary study conducted by the University of Oxford scientists demonstrated that mixing the AstraZeneca and Pfizer vaccines produced a robust immune response against the SARS-CoV-2 (COVID-19) virus and induced higher antibodies than an only two-dose schedule of AstraZeneca vaccine and none of the groups demonstrated decreased neutralizing activity against the Alpha variant (UK variant), but the neutralization titer reduced by 2.5 to 6 times against the Beta variant (South African variant), Gamma variant (Brazilian variant), and Delta variant (Indian variant).*

*The Comparing COVID-19 Vaccine Schedule Combinations (Com-COV) study (463 cases of the 4-week interval group) revealed that immunization with AstraZeneca vaccine followed by Pfizer vaccine at the 4-week interval demonstrated a better immune response out of the two mixed dosing regimens. Com-COV study demonstrated in the earlier phase that around 30 % to 40 % of those who received mixed doses reported fevers after their second jab, compared to 10 % to 20 % of those who received the same vaccine for both doses. This result could be attributable to the shorter, 4-week interval between doses that was used during the Oxford study, whereas the safety data from a cohort with a 12-week dosing interval is still to appear.*

*In conclusion, it is better to give a different COVID-19 vaccine than not administer the second dose at all.*

***Keywords**: COVID-19, mix-and-match, mix, match, vaccine, vaccination*

## Abbreviations:

Com-COV: COVID-19 Vaccine Schedule Combinations,

COVID-19: Coronavirus disease 2019,

HIV: Human immunodeficiency virus,

SARS-CoV-2: severe acute respiratory syndrome-coronavirus type 2,

UK: United Kingdom,

USA: United States of America

### Objectives of The Study

The objectives of this study is aimed to identify the feasibility of mixing and matching COVID-19 vaccination in the situation of shortage of COVID-19 vaccines.

## Methods of the Study

### Search Strategy and Inclusion Criteria

A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including ScienDirect, PubMed, Scopus, ISI Web of Science, and websites of the news. The search was applied to the articles that were published between January 2021 and September 2021. Our first involved performing searches of article abstract/keywords/title using strings of [(“ Mix-and-match covid-19 vaccination ” or “ Mixing and matching ”, “ Vaccination ” and “ COVID-19 ”]. After a first approach of search, published articles focusing on COVID-19 were retained and the information on vaccine type and COVID-19 was extracted for having a crude knowledge involving their themes. Another round of publication search was conducted for adding the missing published articles that were not identified by the first round.

All keywords combinations from one disease type and climatic variable to bind the population of cases under consideration. Search string for disease groups include [ “ SARS-CoV-2 ” or “ COVID-19 ” or “ Vaccination ” or “ Vaccines ” or “ Mixing and Matching ” or “ Mix-and-Match ” ]. The initial literature databases were further manually screened with the following rules : 1) non-human infectious disease-related articles were excluded; 2) articles that did not report mix-and-match vaccination related to COVID-19 were not considered, such as commentary articles, or editorial; 3) non-peer reviewed articles were not considered to be of a scholarly trustworthy validity; and 4) duplicated and non-English articles were removed. The articles were carefully selected to guarantee the literature quality, which is a trade-off for quantity.

With strict literature search and screening processes, it yielded 8 articles from 106 articles of initial literature database. Needed article information was extracted from each article by : 1) direct information including journal, title, authors, abstract, full text documents of candidate studies, publishing year; 2) spatial scale and place name of the study area; 3) study period; 4) research method used; 5) type of COVID-19 vaccine studied; 6) types of mix-and-match vaccination studied; and 7) the conclusions made about the impacts of mix-and-match COVID-19 vaccination types on patients’ COVID-19 outcomes.

## Introduction

In low-income and middle income countries, Ebola vaccine (Johnson & Johnson) experience demonstrated that mix-and-match vaccination is feasible, safety, and long-lasting immunization, adopted in phase I and phase II trials and can overcome easily with active community participation and suitable national planning [1, 2]. In addition to Ebola, this concept has been previously implemented for influenza, malaria, and HIV [2]. The prime dose in the most of the current vaccination regimen is at a month interval followed by a second homologous booster dose [3]. Recent interest in COVID-19 mixing

vaccination is aimed to simplify countries' facing fluctuation of various vaccine supplies and immunization efforts and increase SARS-CoV-2 (COVID-19) protection by delivery of the similar or same antigens of the disease-causing agent via two different vaccine types and eliciting a strong and long-lasting immune response as compared to the single vaccine regimen, but has a lack of evidence and a potential risk of increased-mixing-vaccine-adverse side effects [3] that include increased headache, increased fever, increased malaise, increased joint pain, and increased AEFI, particularly in the elderly population [3].

## Results

With strict literature search and screening processes, it yielded 8 articles from 106 articles of initial literature database. Needed article information was extracted from each article by : 1) direct information including journal, title, authors, abstract, full text documents of candidate studies, publishing year; 2) place name of the study area; 3) study period; 4) research method used; 5) type of mix-and-match COVID-19 vaccination studied; and 6) the conclusions made about the yields of mix-and-match COVID-19 vaccination on human protection of COVID-19.

## Discussion

In June 2021, a preliminary study conducted by the University of Oxford scientists demonstrated that mixing the AstraZeneca and Pfizer vaccines produced a robust immune response against the SARS-CoV-2 (COVID-19) virus and induced higher antibodies than an only two-dose schedule of AstraZeneca vaccine and none of the groups demonstrated decreased neutralizing activity against the Alpha variant (UK variant), but the neutralization titer reduced by 2.5 to 6 times against the Beta variant (South African variant), Gamma variant (Brazilian variant), and Delta variant (Indian variant) [4]. The Comparing COVID-19 Vaccine Schedule Combinations (Com-COV) study (463 cases of the 4-week interval group) revealed that immunization with AstraZeneca vaccine followed by Pfizer vaccine at the 4-week interval demonstrated a better immune response out of the two mixed dosing regimens [4]. Com-COV study demonstrated in the earlier phase that around 30 % to 40 % of those who received mixed doses reported fevers after their second jab, compared to 10 % to 20 % of those who received the same vaccine for both doses. This result could be attributable to the shorter, 4-week interval between doses that was used during the Oxford study, whereas the safety data from a cohort with a 12-week dosing interval is still to appear [4]. The trials in Germany and Spain have also demonstrated that a mixed dosing regimen induced a better immune response than getting two doses of the AstraZeneca vaccine [4]. In South Korea, the study on 100 actually-receiving-mixed-doses cases out of 499 cases conducted by the Korea Disease Control and Prevention Agency on a mixed vaccination, with AstraZeneca vaccine as the first dose and Pfizer vaccine as the second dose revealed the increased neutralizing antibody levels of 6 times higher than those found after two doses of the AstraZeneca jab [4]. Initial phase of Com-COV

study or Com-COV1 study has been concentrated on mixing the AstraZeneca and Pfizer jabs, whereas Com-COV2 study or phase 2 of the Com-COV study is assessing the immunogenicity and safety of combining the Moderna and Novavax vaccines with a first dose of either the Pfizer or AstraZeneca jab [4]. Globally, COVID-19-dose-mixing studies on assessing other vaccine combinations are also ongoing, including a Russian trial of an AstraZeneca-Sputnik V combinations and a Philippines-based study mixing Sinovac' s CoronaVac jab with 6 other vaccines [4]. In India, COVID-19 mixing vaccination can assist in scaling up the vaccination drive to a large extent in this world's-largest-COVID-19-vaccination-drive country [3].

As of June 6, 2021, China, UK, and USA have began the COVID-19-vaccine mixing trials, but have not yet officially approved them due to not being designed to assess actual COVID-19 protection and non-corresponding-COVID-19-real-life protection of the studies' antibody and T-cell measurements, whereas only Canada, Denmark, France, Germany, Norway, and Sweden implemented mixing vaccination to their citizens with rarely reported ChAdOx1 nCoV-19 (AstraZeneca) thromboembolic complications [3, 5]. Whenever it is impossible to provide a second dose of COVID-19 vaccine, the Public Health of England guidelines recommend that it is better to give a different COVID-19 vaccine than not administer the second dose at all [3]. On July 12, 2021, the WHO's chief scientist has suggested individuals against mixing and match in COVID-19 vaccines from different manufacturers [6]. Nevertheless, on July 13, 2021, Thailand defended mixing two different COVID-19 vaccines to fight against a surge in SARS-CoV-2 (COVID-19) infections since COVID-19 outbreak in April 2021 after the WHO's top scientist warned that it was a " dangerous trend " not backed by evidence [5, 7]. Thailand's health authorities will mix a first dose of the Chinese-produced " Sinovac " jab with a second dose of Astrazeneca vaccine to try and achieve a " booster " effect in 6 weeks instead of 12 weeks due to fast spreading disease (more than 353,700 reported- COVID-19-infected cases and 2,847 reported-COVID-19-related deaths in April 2021) [7]. Figure 1 [8], Table 1 [8] and 2 [3] demonstrate different platforms of COVID-19 vaccines and mechanisms of antigen presentation, advantages and disadvantages of various platforms of COVID-19 vaccines, and recently published clinical trials and ongoing clinical trials on mixing COVID-19 vaccination( as of July 11, 2021), respectively.

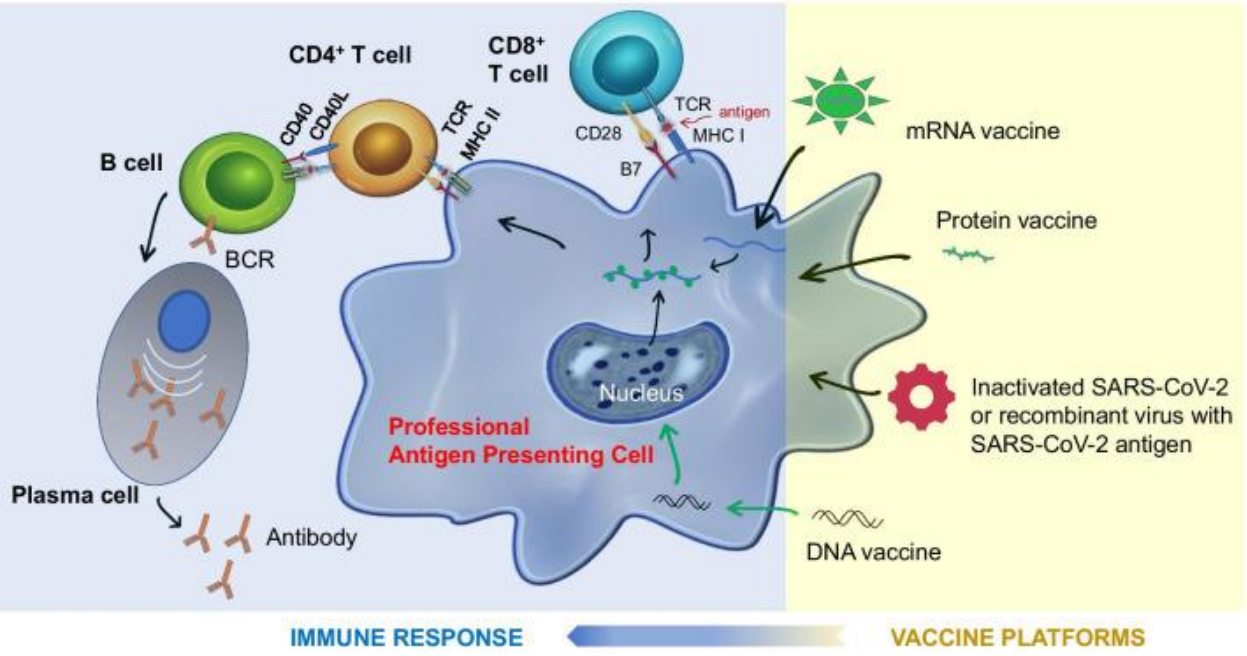


**Figure 1** : Different platforms of COVID-19 vaccines and mechanisms of antigen presentation, and protective immunity generation

(**Source** : Hwang JK, Zhang T, Wang AZ, Li Z. COVID-19 vaccines for patients with cancer : benefits likely outweigh risks. Journal of Hematology and Oncology 2021; 14 : 38. DOI : https://doi.org/10.1186/s13045-021-01046-w [8])

| Vaccine Platform | COVID-19 Vaccines (approved/in development) | Advantages | Disadvantages |
|---|---|---|---|
| Inactivated Virus | SinoVac (CoronaVac + aluminum)<br>Sinopharm (Inactivated whole virus SARS-CoV-2 + aluminum) | Prior experience and technology, e.g., quadrivalent influenza vaccine<br>Easier storage, does not need to be frozen<br>Entire virus, with all antigens presented | Poor inducers of CD8+ T-cell immunity<br>Need adjuvants to boost<br>Large batches of live virus pose biosecurity risk |
| mRNA | Pfizer/BioNTech (BNT162b2) | Unable to integrate into host genome<br>Delivery into host cytoplasm<br>Avoids introducing pathogen (SARS-CoV-2)<br>Avoids anti-vector immunity<br>Easier mass-production | Frozen for vaccine storage<br>Needs delivery of lipid nanoparticle |

| | | | |
|---|---|---|---|
| | | Elicit strong humoral and cellular immunity | |
| DNA | Inovio (INO-4800) | Avois introducing pathogen (SARS-CoV-2)<br>Easier mass-production<br>Mimics natural infection<br>Elicits strong humoral and cellular immunity | Delivery into nucleus of host cell |
| Protein subunits | Novavax (NVX-CoV2373)<br>Vector Institute (EpiVacCorona) | Does not introduce pathogen (SARS-CoV-2)<br>Being able to focus on antigens that generate neutralizing antibodies | Lower humoral and cellular immunity response<br>Not efficiently presented<br>Require adjuvants to boost<br><br>Produced *ex vivo* may not retain post-translational conformation or modifications |
| Replication incompetent adenoviral vector | AstraZeneca (ChAdOx1 nCoV-19/AZD1222)<br>Johnson and Johnson (Ad26.COV2.S)<br>CanSino Biologics (Ad5-nCoV)<br>Gamaleya (Sputnik V) | Mimics natural infection<br>Avoids pathogen (SARS-CoV-2)<br>Elicits humoral and cellular immunity<br>No new viral particles (Defective Replication) | Lower efficacy if prior anti-vector immunity exists<br>Anti-vector immunity may interfere |

**Table 1** : Demonstrating advantages and disadvantages of various COVID-19 vaccine platforms

(**Source** : Hwang JK, Zhang T, Wang AZ, Li Z. COVID-19 vaccines for patients with cancer : benefits likely outweigh risks. Journal of Hematology and Oncology 2021; 14 : 38. DOI : https://doi.org/10.1186/s13045-021-01046-w [8])

| **Ongoing Clinical Trials** | | | | |
|---|---|---|---|---|
| **Site/Number of Participants** | **Current Status (As of July 11, 2021)** | **Type and Clinical Trial Objective** | **Group and Vaccine Type** | **Primary and Secondary Outcomes** |

| | | | | |
|---|---|---|---|---|
| Austria (NCT04907331)/ 3,000 participants | Ongoing | Randomized, Controlled Trial,phase II; evaluating safety and efficacy of heterologous vaccination with ChAdOx1-S, AZ (Vaxzevria) followed by BNT162b2, Pfizer/BioNTech) (Comirnaty) | Clinical Trial Arm: Prime: ChAdOx1-S or ChAdOx1 nCoV-19 vaccine, AZ (Vaxzevria); Boost: BNT162b2 vaccine, Pfizer/BioNTech (Comirnaty) 12 weeks apart Control Arm: Homolog Vaccination with Vaxzerria (Prime/Boost) or Comirnaty (Prime/Boost) | Primary Outcomes: T-cells response to SARS-CoV-2 (COVID-19) Spike Protein Epitopes in both arms; Neutralizing Antibodies in both arms; Vaccine Failures in both arms |
| China (NCT04892459)/ 300 participants | Ongoing | Randomized, Paralell-Controlled Clinical Trials; evaluating safety and immunogenicity of sequential immunization of a recombinant SARS-CoV-2 (COVID-19) vaccine (Adenovirus Type V Vector) | Clinical Trial Arm: Prime: Inactive SARS-CoV-2 (COVID-19) (Vero cell) (Sinovac Research & Development Co., Ltd); Boost: Recombinant SARS-CoV-2 (COVID-19) Ad5 Vectored Vaccine (CanSino Biologics); Comparator Arm: Homogeneous Boost Arm with Inactive Vaccine | Primary Outcomes: Adverse Reactions within 28 days after the booster dose; Genomic Mean Titer (GMT) of Neutralizing Antibodies against Live SARS-CoV-2 (COVID-19) Virus on Day 14 after Booster Dose |
| France (NCT04900467)/ 400 participants | Ongoing | Randomized, Open Label, Non-Inferiority Clinical Trial | Arm 1: Prime: Pfizer/BioNTech mRNA Vaccine; Boost: Moderna mRNA Vaccine versus Prime: Pfizer/BioNTech mRNA Vaccine; Boost: Pfizer/BioNTech mRNA Vaccine Arm 2: Prime: Moderna mRNA Vaccine; Boost: Pfizer/BioNTech mRNA Vaccine versus Prime: Moderna mRNA Vaccine; Boost: Moderna mRNA Vaccine | Primary Outcomes: Anti-Spike IgG Titer 28 Days following Vaccination in both arms Secondary Outcomes: Adverse Events |
| Canada (MOSAIC) (NCT04894435)/ | Ongoing | Randomized Clinical Trial; evaluating the immune | Multiple Groups (13) comparing Various Combination of Moderna mRNA vaccine and | Primary Outcomes: Antibody Response to SARS-CoV-2 (COVID-19) Spike Protein at |

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| 1,300 participants | | response and safety of two different vaccines for the first and second doses and differing between the first and second doses of the two-dose vaccines | ChAdOx1 nCOV-19 (AstraZeneca) vaccine in homologous and heterologous prime-boost regimens | 28 Days following Second Dose of Vaccine; Secondary Outcomes: Pseudo neutralization Assay, T-Cell Testing, Antibody-Dependent Cellular Cytotoxicity (ADCC), Antibody Avidity; Description of Safety Outcomes Over 12 months post-vaccination including serious adverse events (SAEs); Incidence of Grade III solicited local and systemic adverse events, SAEs, AEFIs, within 7 days after vaccination; Durability of Antibody Response to SARS-CoV-2 (COVID-19) Spike Protein over 12 months |
| USA (National Institute of Health (NIH) Trial) (NCT04889209)/ 400 participants | Ongoing | Phase I/II, Open-Label Clinical Trial; evaluating safety, reactogenicity and immunogenicity of a delayed (> 12 weeks) vaccine boost | Vaccines: Ad26.COV2. S (Janssen Pharmaceuticals/Johnson & Johnson), BNT162b2 (Pfizer/BioNTech), or mRNA-1273 (ModernaTX); Boost: Booster shot following complete vaccination will be provided in various combinations via multiple arms of the clinical trial | Primary Outcomes: Response Rate of SARS-CoV-2 (COVID-19) Specific Antibody Binding and Neutralization Titers; Occurrence of SAEs after Last Dose on the clinical Trial and after Delayed Booster Vaccination; Magnitude of SARS-CoV-2 (COVID-19) Specific Antibody Binding and Neutralization Titer |
| **Published Clinical Trials** | | | | |
| Site/Authors/Clinical Trial Name/Number of Participants | Type of Clinical Trial | Group and Vaccine Type | Clinical Trial Outcomes | Adverse Events |
| Germany/GroB *et al*/26 participants | Prospective, Observational Clinical Trial | First Dose: ChAdOx1 nCoV-19 vaccine (AstraZeneca) Second Dose: | CD4+ and CD8+ T Cells Reacts to SARS-CoV-2 (COVID-19) Spike Peptide Stimulus 2 Weeks Post-Full Vaccination; Neutralizing Activity Against Prevalent Strain | Prime Dose: Mild to Moderate Reaction (88.4 %) Boost Dose: Mild or Moderate Symptom (80.8 %) Common Symptoms: |

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| | | BNT162b2 vaccine (Pfizer/BioNTech) following 8-week interval No Control Group | B.1.1.7 (Alpha Strain) with Hetrologous Prime Boost was 3.9 times higher than in persons receiving Homologous BNT162b2 vaccination (Pfizer/BioNtech); Strong Neutralization Titers 2 Weeks Post-BNT162b2 vaccine (Pfizer/BioNTech) boost | Pain at the injection site, Fever, Headache, Chills, Myalgia, Fatigue |
| Germany/Hillus *et al*/340 participants | Prospective, Observational Cohort Study | Trial Arm 1: Prime: ChAdOx1 nCoV-19 vacccine (AstraZeneca); Boost: BNT162b2 vaccine (Pfizer/BioNTech 10-12 weeks apart Trial Arm 2: Homologous BNT162b2 vaccine (Pfizer/BioNTech) (prime and boost) 3 weeks apart | T-cell Reactivity: Significantly higher following Heterologous ChAdOx1/BNT162b2 boost compared to Homologous BNT162b2/BNT162b2 boost; S1-IgG Avidity: High following Heterologous ChAdOx1/BNT162b2 boost compared to Homologous BNT162b2/BNT162b2 boost; Neutralizing Antibody Response 3 weeks post-boost immunization: Homologous BNT162b2 (99.01 %), Heterologous ChAdOx1/BNT162b2 boost (100.0 %); Serum Antibody Response: Strongly Increased following both Homologous and Heterologous boost | Local eaction : Slight higher frequency following Heterologous ChAdOx1/BNT162b2 booster compared to Homologous BNT162b2/BNT162b2 booster Systemic Reactions: Most frequent following prime immunization with ChAdOx1 (86 %) and less frequent following Homologous BNT162b2/BNT162b2 (65 %) or Heterologous ChAdOx1/BNT162b2 booster vaccination (48 %); No potential life-threatening reactions following any of the COVID-19 vaccine regimens |
| Spain/Borobia *et al*/663 participants | Randomized, Phase II Trial | Trial Arm: Prime: ChAdOx1 nCoV-19 vaccine (Vaxzevria, AstraZeneca); Boost: BNT162b2 vaccine (Comirnaty, Pfizer/BioNTech) Control Arm: Received only one dose and not received | Trial Arm: Greater Immune Response: 150 times antibody 14 Days following Second Dose; 4 times increase in Cellular Immune Response; Effective in Protecting Against SARS-CoV-2 (COVID-19) Control Arm: Antibody Titers at 14 Days similar to Baseline Titers | Similar in both groups: Mild (68.3 %); Moderate (29.9 %) Most Common: Headache (44 %); Malaise (41 %); Chills (25 %); Mild Nausea (11 %); Mild Cough (7 %); and Fever (2.5 %) |

| | | | | |
|---|---|---|---|---|
| | | any second dose of vaccine | | |
| UK/Shaw *et al*/830 participants | Single-Blind, Randomized, Phase II Trial | Trial Arm 1: Prime: ChAdOx1 nCoV-19 vaccine (Vaxzevria, AstraZeneca); Boost: BNT162b2 vaccine (Comirnaty, Pfizer/BioNTech) Trial Arm 2: Prime: BNT162b2 vaccine (Pfizer/BioNTech); Boost: ChAdOx1 nCoV-19 vaccine (AstraZeneca) Control Arm: Homologous Schedule: Arm 1: Prime and boost: BNT162b2 vaccine (Pfizer/BioNTech); Arm 2: Prime and boost: ChAdOx1 nCoV-19 vaccine (AstraZeneca) | Not yet reported | Greater Systemic Ractogenicity in Heterologous prime-boost regimen than their Homologous counterparts; Most common symptom: Feverishness No hospitalization Most of increased Reactogenicity identified within 48 hours following immunization |

**Table 2:** Demonstrating recently published clinical trials and ongoing clinical trials on mixing COVID-19 vaccination, as of July 11, 2021.

(**Source:** Adapted from: Kunal S, Sakthivel P, Gupta N, et al. Mix and match COVID-19 vaccines: potential benefit and perspective from India. Postgrad Med J 2021. DOI: 10.1136/postgradmedj-2021-140648 [3])

## Conclusion

It is better to give a different COVID-19 vaccine than not administer the second dose at all.

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