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Heterologous Prime-boost Approach for COVID -19 Vaccine - A Light at the End of the Tunnel?

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Abstract

COVID -19 disease has emerged as a health crisis globally. The absence of specific antiviral treatment to cure COVID-19 has emphasized the importance of providing a safe and effective vaccine, they are the best bet to save millions of lives. The heterologous prime-boost approach for the COVID-19 vaccine is in the limelight as it can overcome issues with the shortage in the supply of vaccines and enhances the antibody response and potency of the prevailing COVID-19 vaccines, thus helping the acceleration of COVID -19 vaccine drive throughout the globe to achieve herd immunity among the population. This review aims to discuss the history, mechanism, and current scenario of the application of the heterologous prime-boost approach for the COVID-19 vaccine. From data inception to August 2021, Scopus, Web of Science, PubMed, WHO worldwide research on COVID-19, and the clinical trials registration "https://clinicaltrials.gov/" were used to conduct the systematic search by using keywords: "COVID-19,"heterologous," and "vaccine." The heterologous prime-boost vaccination approach seems to be a silver lining that has the potential to ensure the suitable vaccine is delivered to the right people during times of pandemic.

Keywords: *COVID -19, Heterologous, Prime-boost Approach, Vaccine*

Introduction

The highly infective second wave of COVID -19 has made the first wave which started to decline from September 2020 as a ripple in the bathtub, with a devastating impact on many countries [1]. Its spread was highly unprecedented India, the country with the second-largest population globally, recorded 26 million COVID-19 cases in the month of May 2021, second only to the United States of America, and became a new epicentre for the global pandemic [2]. With the decrease in cases from July 2021, India is emerging from the deadly second wave of COVID -19. The daily cases of COVID19 have begun to rise again, almost a month after the second wave was deemed to be over. India recorded a total number of 3, 25, 58,530 cases on August 25, 2021 [3]. Rural India had escaped the COVID-19 fury in the first wave, but now it's increasing at a rapid pace across rural districts, with the biggest number of cases been recorded in Maharashtra, Uttar Pradesh, Karnataka, Kerala, and Andhra Pradesh [4]. Due to the non-availability of specific antiviral treatment to treat COVID -19, practices to prevent transmission of the disease and mass vaccination are the two primary weapons to fight the battle against this deadly disease [5].

The vaccination drive in India, which is considered one of the largest in the world, was initiated on January 16, 2021. Two major vaccines available in India are the recombinant Covishield and whole inactivated Covaxin [6]. The department of ministry of health and family welfare, the Government of India, reported a total of 603846475 vaccination doses in India as of August 26, 2021, which does not account for even half of its population. Breakthrough infections of COVID-19 occur as the vaccine does not provide 100% protection against the disease, but it is less virulent in the vaccinated individuals [7]. As of June 3, 2021, WHO has approved six vaccines for use that have met the criteria for safety and efficacy [8]. Therefore immunity through vaccination to achieve herd immunity is the need of the hour to decrease the burden of the disease and speed up the economic recovery [9]. The inception of new variants of SARS Co-V-2 and waning antibody levels in the vaccinated population has raised concerns over the effectiveness of first-generation vaccines, which were approved for use during the crisis [10].

The presently in-use mRNA vaccines (BNT162b2 and mRNA-1273) have conferred >90% protection against COVID-19 infection, but the few reported undesirable effects have inflated potential concerns about the safety of these vaccines. These mRNA vaccines also need strict storage conditions (cold chain requirement), posing a crucial logistical challenge, especially in developing countries [11-13].

Inactivated and recombinant protein-based vaccines reported fewer adverse reactions, but the main disadvantage is they conferred lower immunogenicity [14–16]. Adenovector-based vaccine (Ad-5 vectored vaccine) induces potent T-cell responses but fails to elucidate effective antibody response [17]. The heterologous prime-boost approach is considered to be a silver lining, especially for developing countries like India where this approach may help to reduce the overwhelming logistics of immunizing millions of population and affectively boost the immune response.

Brief Literature Search

This narrative review highlights a brief non-systematic methodology to include the selected articles for discussion. A systematic search of Scopus, Web of Science, Pubmed, WHO global research on COVID-19 and the clinical trials register "https://clinicaltrials.gov/" databases was done from data inception to August 2021 using the following MeSH terms (Coronavirus disease 2019 or COVID 19), SARS- CoV-2, "heterologous" AND "vaccination" and trained immunity. Only published articles in English were included.

Evolution of Heterologous Prime-Boost Vaccination

Heterologous prime-boost vaccination approach was first employed on a non -human primate model. It was reported in Landmark Science report in the year 1992 [18], which provided a breakthrough in the early attempt to develop an HIV vaccine where Macaca fascicularis was immunized with recombinant vaccinia virus that expresses SIV mne gp160 protein produced in baculovirus-infected cells which on animal models showed a promising effect of protection from the intravenous challenge of SIV

mne virus [19]. Girard et al reported an strengthening immune response in an chimpanzee which was inoculated with a recombinant vaccinia virus vaccine as a priming dose followed by multiple booster doses of an a mixture of recombinant HIV-1 proteins or synthetic peptides [20]. Recombinant vaccinia virus containing HIV-1 Env gene was used as a priming dose followed by booster dose of recombinant Env protein for testing heterologous prime-boost vaccination on humans for the first time [21]. Invention of DNA vaccines in the year 1990 opened a new era for HIV-1 vaccine development effort where DNA vaccines were used as priming doses followed by booster doses of other forms [22, 23].

The heterologous prime-boost vaccination approach gained momentum against many pathogens. Malaria was a disease with a high mortality rate for which the invention of an efficacious vaccine was crucially needed. Li et al described a study in which mice was immunized with a recombinant vaccinia and a recombinant influenza virus vaccine, this heterolgous approach elicited a potent immune response against malaria and opened a new era for introducing malarial vaccines [24]. Dunachie SJ et al. in his study, concluded that DNA prime -MVA boost vaccine encoding thrombospondin -related adhesion protein produced a partial immunity against Plasmodium falciparum sporozoite in healthy malaria naive adults [25]. Sulyok Z et al. reported the heterologous approach for malarial vaccine PfSPZ-CVac regimen is effective, secure, acceptable, and induced a potent immune response [26].

The Ebola virus epidemic took a toll in West Africa, costing the lives of thousands and causing a severe economic crisis. Venkatraman N et al. conducted a clinical trial on healthy adults in the age group of 18-50 years to assess the safety and the ability to induce immune response of a modified vaccinia Ankara virus vectored Ebola Zaire vaccine (MVA-EBO-Z) alone and the heterologous prime-boost regimen of ChAd3- EBO-Z recombinant chimpanzee adenovirus type 3 vectored Ebola Zaire vaccine (ChAd3-EBO-Z) followed by MVA-EBO-Z. This approach was well tolerated and resulted in potent cellular and antibody response [27]. Goldstein N et al. conducted a study to assess the safety and potency of 2 dose regimens of Ad26.ZEBOV (adenovirus serotype 26 [Ad26]) and MVA-BN-Filo (modified vaccinia Ankara [MVA]) vaccines with booster priming on day 360. Both homologous and heterologous approaches were acceptable irrespective of dose and interval. Heterologous 2-dose Ad26, MVA approach induced a more potent immune response that paved a way for potential use of this vaccine for treatment of Ebola virus infection [28].

The BCG (Bacille Calmette - Guérin) vaccine is among one of the oldest and most widely used vaccinations in the world against mycobacterium tuberculosis. BCG vaccine has shown to have a protective efficacy against virus, bacteria, and parasites through heterologous lymphocyte activation [29].

Mechanism of Heterologous Immunization

Induction or modification of immune response by one pathogen against another unrelated pathogen is heterologous immunity [30].

- **Antigen Cross-reactivity**

Innate immune cells have a broad recognition pattern. Lymphocytes have a property of cross-reactivity for antigen identification which plays a vital role to induce heterologous immunity [31]. T-cells with a T-cell receptor (TCR) for a specific peptide epitope (eg: CD8~9 amino acid and CD4 ~11aminoacid) is present in an individual much earlier than getting exposed to that specific foreign antigen [32]. Surprisingly, T-cells respond to a wide spectrum of infections to give protective immunity, despite the fact that they are thought to be individually specific. To maintain T and B cells in full gear, each T-cell clone type must identify roughly 106 p-MHC combinations [33, 34].

CD 8+ and CD 4+ T cells recognize peptide epitopes of 9-16 amino acids in the context of MHC class I and class II molecules, respectively. Only 3-5 amino acids of the peptide bond are in contact with MHC molecules via the T-cell receptor, and at least 4 amino acid length peptides have been demonstrated to induce T cell activation [35, 36]. Binding of TCR with p-MHC complex is mediated by weak inter-molecular bond, i.e. Van der Waals forces, therefore, resulting in decreased affinity of

interaction [37]. Cross-reactivity of T-cell receptors is also caused by rearrangements in the structure and conformational plasticity of the binding top-MHC complex, differences in angles of docking onto p-MHC, conformational shifts in both peptide and MHC of the p-MHC complex, structural degeneracy of amino acids in the peptide bound to MHC, and structural degeneracy of amino acids in the peptide bound to MHC [38] (Figure 1).

- **Bystander Activation of Unrelated Lymphocytes**

Non -specific polyclonal activation of T lymphocytes or antibody producing B lymphocytes is triggered by components of microbes or inflammatory cytokines [39].

The antigen peptides provided by large histocompatibility complex class II molecules bind to the T-cell receptor (Signal 1), T-cell activation is controlled by activation of costimulatory molecules (signal 2), which then differentiate into discrete subsets of helper T cells in different cytokine milieus (signal 3), as characterised by their effector cytokine output [40, 41]. T-cell receptor signalling is not required for bystander T-cell activation [42]. Toll-like receptors (TCRs) and various interleukin 1(IL-1) family cytokines (IL-1,IL-11,IL-18) as well as signal transducer and activator of transcription (STAT) activators (IL-2, IL-12), I (IL-23), and I (IL-27) emerge to play a significant role in TCR-independent bystander activation, with effector/memory CD+4 cells being more probable to be activated by this process [43] (Figure 2).

- **Trained Immunity**

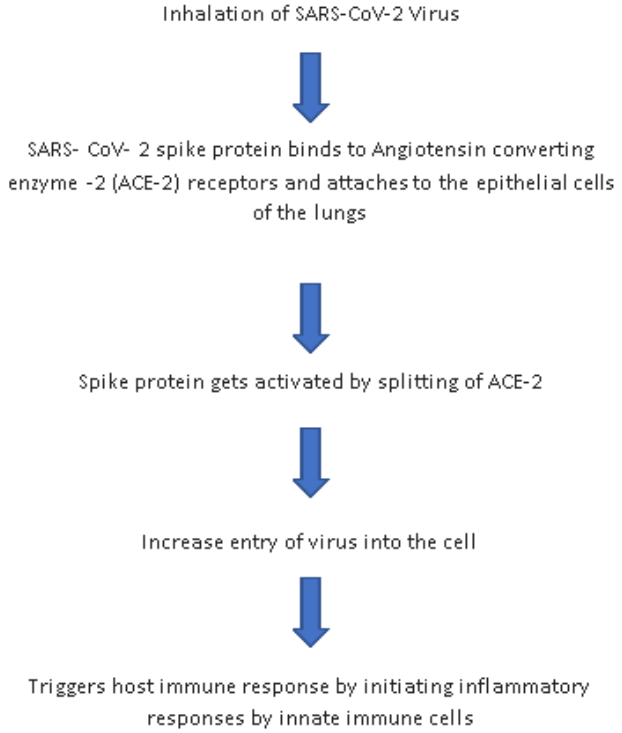
"Trained immunity" refers to non-specific protection against infection mediated by epigenetic programming of innate immune cells that is triggered by stimuli and results in a modified responsiveness to a second challenge. Traditionally it was believed that innate immune cells did not exhibit adaptive characteristics. Alteration in the DNA methylation status and accumulation of chromatin marks leads to the unfolding of chromatin which accelerates the transcription process and increases the production of proinflammatory factors. After the stimulus is removed, these alterations are only partially removed from the innate immune cells, allowing for increased activation of transcriptional regulators and gene function [44] (Figure 3).

Availability/non-availability of intermediates of TCA cycle regulate this process as these intermediates play a pivotal role as regulatory signals for epigenetic enzymes [45].

Heterologous Prime-Boost Strategy of Covid-19 Vaccines as Magic Bullets

- **Current Scenario of Heterologous Prime-boost Approach**

Providing appropriate vaccines to the potential candidates at the right time in a densely populated country like India is a significant potential logistical challenge. Currently, the available vaccination protocol involves a second homologous dose as a booster following an initial prime-boost. The recent interest in applying the heterologous prime-boost approach (Mix and Match) for COVID -19 vaccines has paved a new way in easing immunization efforts by countries with fluctuating vaccine supplies and its sensible utilization to benefit population across the world [46].



A rational immune-based treatment should be employed depending on the phases of COVID-19 infection. Enhancing the innate immune response to regulate viral replication in the initial phase of the disease and breaking the hyper inflammatory loop to prevent severe complications later. Inducing innate immunity by heterologous vaccine approach before infection may prove as an effective approach. Studies have shown promising effects in the treatment of COVID-19 by using a heterologous vaccination approach (Table 1).

- **Adverse Reactions of Heterologous Prime-boost Approach**

Mild symptoms such as myalgia, fever, tiredness, joint pain were reported. Routine prophylactic use of paracetamol may alleviate these symptoms. Biochemical and hematological profiles were identical between homologous and heterologous vaccine approaches [53].

Conclusion

The heterologous prime-boost vaccine approach might be a panacea for the 'just very humiliating' disparity in global vaccine availability. It will pave the way for accelerating the vaccination drive in many countries and ensures every eligible individual receives two doses of vaccine they deserve without fail. Ongoing studies on efficacy, safety, and reactogenicity of the heterologous prime-boost approach of COVID -19 vaccines provide promising evidence that the heterologous prime-boost approach for COVID-19 vaccine will soon be a reality and benefit every nation to achieve the much needed herd immunity to curb this pandemic.

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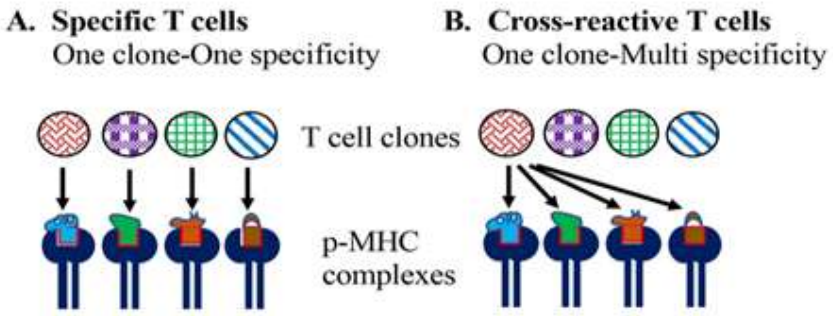
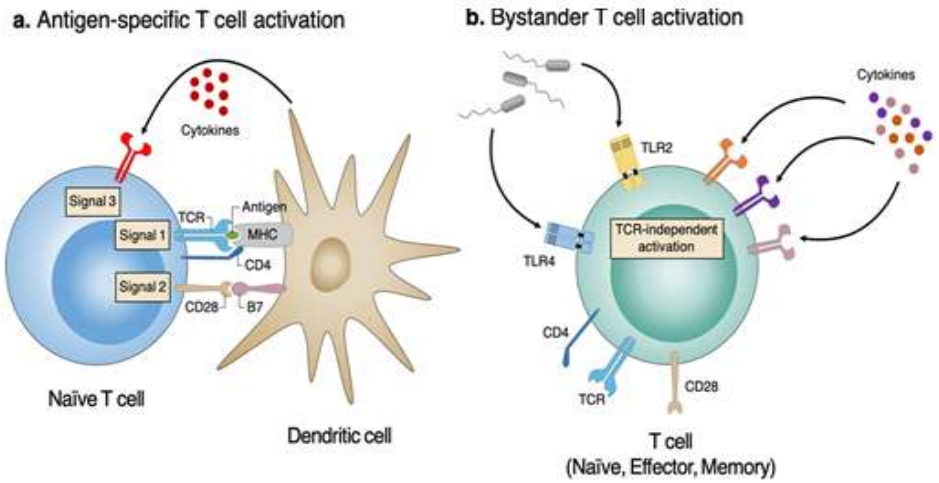


A) T-cell Specificity: Individual T-cell Clones Recognize Specific Peptide Epitope

B) Cross Reactivity: T-cells can Recognize Many Peptide Epitopes

Figure 1: Specificity v/s Cross Reactivity of T- cells



a. Signal 1: Engagement of peptides furnished by MHC complex molecules to the T- cell receptor

Signal 2: Interaction of CD 28 with B7 molecules (CD 80 and CD 86)

Signal 3: Polarizing signalling by cytokines produced by dendritic cells

b. Independent of T-cell receptor activation, responds swiftly to mediators of inflammation

Figure 2: Antigen-specific vs. Bystander T-cell Activation

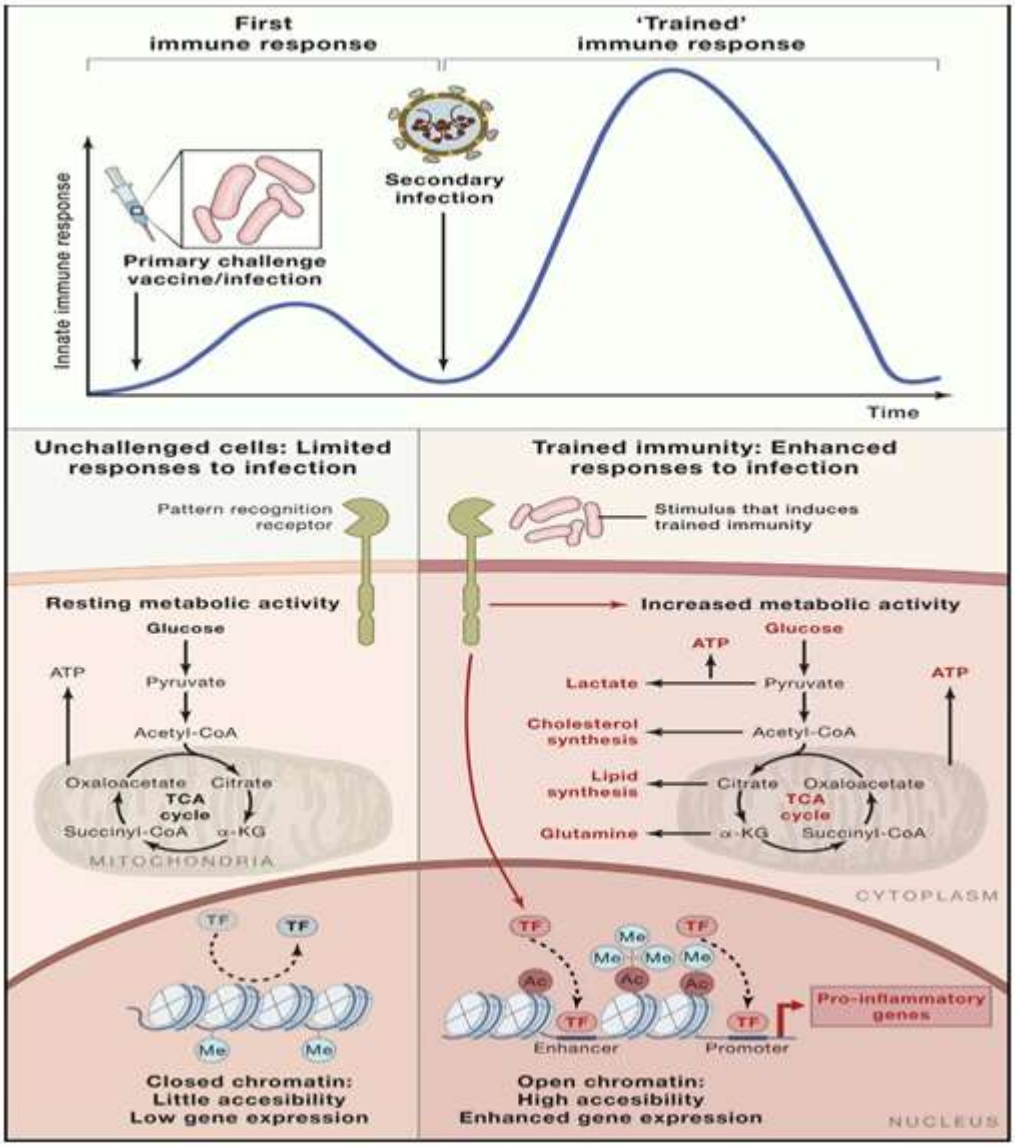


Figure 3: Metabolic and Epigenetic Changes Mediated during Trained Immunity

Author	*Methodology*	*Outcome*	*Conclusion*
He Q [10]	Heterologous prime boost approach using four different types of vaccines(adenovirus vector based, inactivated vaccines, mRNA vaccines and recombinant protein vaccines, by different manufacturers were tested on mouse models	Increased humoral antibody response was elicited with adenovirus vectored vaccine followed by inactivated/recombinant subunit/mRNA vaccine administration. Heterologous prime boost regimen with adenovirus vector vaccine increased the Th-1 based T- Cell responses	Heterologous vaccine approach in murine models elicited enhanced levels of neutralizing antibodies which was to be tested in human studies
Hillus D *et al* [47]	Prospective observational study on healthcare workers in Berlin (Germany) was conducted to compare the ability of heterologous immunizations with ChAdOx1 nCov-19 vaccine (AstraZeneca, Cambridge, UK) and BNT162b2 (Pfizer-BioNtech, Mainz, Germany), with homologous BNT162b2 and ChAdOx1 nCov-19 immunization to induce an effective immune response.	The heterologous ChAdOx1 nCov-19–BNT162b2 immunization with 10–12-week interval, was well accepted and provides an effective immune response.	Heterologous prime boost approach recommended in Germany might be generally applicable
Liu X *et al.* [9]	Single blinded randomized clinical trial on individuals aged 50 years and above with no/well controlled comorbidities and no evidence of past COVID-19 infection to assess the safety and immunogenicity of heterologous schedules with the(ChAdOx1 nCoV-19, AstraZeneca) ChAd and (BNT162b2, Pfizer–BioNTech) BNT vaccines.	SARS-CoV-2 IgG concentration in the individuals who received heterologous combination of vaccine was higher than homologous vaccination, the heterologous approach also showed a promising efficacy against preventing severe disease.	ChAd/BNT had a higher immunogenicity when compared with ChAd/ChAd thereby supporting the flexibility of using this approach.

Ostadgavahi AT *et al.* [48]	Two participants were tested for neutralising antibodies after receiving the Covishield (Oxford–AstraZeneca) vaccine and a second (booster) shot of the Pfizer-BioNTech vaccine 33 days later.	Following vaccination, antibodies (IgG, IgM) against the spike protein of the SARS-CoV-2 virus increased, with higher reactivity with the spike protein's receptor binding domain (RBD).	The Pfizer-BioNTech vaccine's heterologous prime boost technique to increasing immunity following first Covishield inoculation was verified.
Tenbusch M *et al.* (49)	Non blinded , non-randomized study to assess the immune response elicited by heterologous vaccine scheme involving ChAdOx1 nCoV-19 as prime and BNT162b2 mRNA (BioNTech-Pfizer) as boost vaccination when compared with homologous vaccination with BNT162b2 or ChAdOx1 nCoV-19 vaccination regimens, respectively .	Increased neutralization activity was observed with heterologous vaccination approach than homologous ChAdOx1nCoV-19 or homologous BNT162b2 vaccination.	Heterologous vaccine approach increases the flexibilty especially when vaccine shortage is encountered. Safety and clinical efficacy of these vaccines needs to be elucidated
Schmidt T *et al.* [50]	Observational study to assess safety and immunogenicity of heterologous priming with the ChAdOx1 nCoV-19 vector vaccine followed by boosting with a messenger RNA vaccine (BNT162b2 or mRNA-1273)	When compared to a homologous vector vaccine, the levels of spike-specific IgG, neutralising antibodies, and spike-specific CD4 T cells were much greater in the heterologous vaccine regimen.	Strong cellular and antibody mediated immune response is mediated by heterologous prime boost vaccination with acceptable reactivity.
Grob R *et al.* [51]	Immune response after a heterologous ChAdOx1 nCoV-19 / BNT162b2 prime-boost vaccination was assessed on a cohort of 26 individuals.	No serious adverse effects were found following heterologous ChAdOx1 nCoV-19 / BNT162b2 vaccination. A potent antibody and T- cell response is elicited against all the variants	The level of immunogenicity and protection offered by heterologous vaccination at least matches that of homologous vaccination regimen.

Borobia M *et al.* [52]	Reactogenecity and ability to induce immune response by heterologous combination of vaccine BNT162b2 (Comirnaty, BioNTech, Mainz, Germany) administered as second dose in participants primed with ChAdOx1-S (Vaxzevria, AstraZeneca, Oxford, UK)was assessed by an open-label randomized control trial on adults between 18-60 years .	A strong immune response was elicited in individuals who were given ChAdOx1-S as a prime dose followed by BNT162b2 as a second dose.	Potent immune response is produced by heterologous approach with acceptable reactivity.

Table 1: Overview of Studies on Heterologous Approach of COVID -19 Vaccine