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COMMENTARY

Heterologous prime-boost vaccination against COVID-19: is it safe and reliable?

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ABSTRACT

Throughout the globe, many nations are struggling to cope with the consecutive waves of the COVID-19. Several vaccines have been employed to overcome this ongoing pandemic and are available as single and double-dose inoculations; however, homologous vaccine efficacy is being reconsidered due to the rapidly emerging SARS-CoV-2 variants. Many studies have been conducted on the heterologous prime-boost vaccine regimens and have shown good efficacy results against COVID-19. This article aims to highlight the safety and reliability of heterologous prime-boost vaccination against COVID-19. We have also made some recommendations towards using these combinations of vaccines for the global mitigation of the subsequent waves of COVID-19.

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1. Introduction

The whole world is striving to recuperate from the consecutive waves of coronavirus disease 2019 (COVID-19)[1,2] caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[3,4] that initially emerged in China in late 2019.[5] To overcome this pandemic, the global efforts are underway for the evaluation of heterologous prime-boost vaccine strategies against COVID-19 so that mass vaccination may be achieved on time besides ensuring the worthwhile efficacy of these vaccines against the SARS-CoV-2 variants.[6] The vaccines supply shortage is one of the significant problems for attaining speedy vaccination across the globe. In the developing countries which depend on donations for vaccine supply, the shortage is an existential issue. Even some developed countries have faced the same deficit in vaccine supply. Therefore, the heterologous prime-boost COVID-19 vaccination may act as a feasible option for the prompt immunization of the susceptible population.

Previously, the heterologous prime-boost regimens have been extensively applied in the (human immunodeficiency virus) HIV vaccination. It has been reported that heterologous prime-boost vaccines can yield intensive and extensive immune responses.[7] The Oxford/AstraZeneca vaccine (ChAdOx1 nCoV19 adenovirus-based vector-vaccine) and Pfizer BioNTech (BNT162b2, COVID-19 mRNA vaccine) and Moderna vaccines (BNT162b2 or mRNA-1273 mRNA-based vaccines) are among the most commonly distributed vaccines worldwide. These vaccines have shown an excellent immunogenic response and remarkably effective specific immune response for preventing infection with the SARS-CoV-2 virus.[8] An efficacy of 63% for the AstraZeneca vaccine, 95% for Pfizer BioNTech vaccine, and 94% for the Moderna vaccine have been reported against COVID-19,[9–11] although the surveillance and analysis of vaccine effectiveness against new SARS-CoV-2 variants continues.

This commentary aims to highlight the safety and efficacy of the heterologous prime-boost immunization to achieve faster roll-out of the COVID-19 vaccines globally and attain a more intense immune response besides the potential prevention of some adverse effects rarely associated with certain homologous prime-boost vaccines.

2. Available SARS-CoV-2 vaccines efficacy and safety

At the beginning of the pandemic last year, developing an effective vaccine was a top global priority.[12] The timeline for the development of the candidate vaccine was much shorter than usual for the vaccine and drug discovery. The entire world was expecting to develop a compound quickly, implement high investments, and employ logistics and biotechnological expertise in a racing process to develop a vaccine.

The initial SARS-CoV data regarding the use of spike proteins as a potential target aided advances in COVID-19 vaccine development.[13] This was facilitated by the use of immunoinformatics for identifying many epitopes using in-silico techniques. The aim was to introduce an immunogenic protein of the virus to the host immune system for triggering a specific immune response; therefore, mRNA vaccines that use a spike protein-encoding mRNA to be translated into the host cells

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were developed (Moderna and Pfizer/BioNTech) and found to be highly efficacious. In contrast, viral-vector-based (adenovirus-based) vaccines (Oxford/AstraZeneca and Janssen Pharmaceutical), as well as inactivated-viral-vaccine (Sinovac), were also developed and revealed promising results.[14]

The technology and mechanisms of vaccines that have been distributed and employed globally against COVID-19 include mainly the adenovirus-based, mRNA-based, and inactivated viral vaccines. Meanwhile, in some vaccines such as the ChAdOx1 nCoV-19 vaccine, some adverse effects such as immune thrombosis and thrombocytopenia syndrome have been reported infrequently in 1–2 per 0.1 million vaccinated persons.[15,16]

Similarly, the incidence of immune thrombosis has also been recorded in patients vaccinated with Ad26.CoV2.S COVID-19 vaccine (Johnson & Johnson).[17] Consequently, the administration of the AstraZeneca vaccine was discontinued temporarily in March 2021 by German authorities due to the incidence of vaccine-induced immune thrombotic thrombocytopenia.[8] The pathogenesis of vaccine-induced thrombocytopenia syndrome has been related to antibody reaction with factor 4 in platelets.[15,16,18] Such antibodies are supposed to be produced in high numbers in response to boosting with adenoviral vector; therefore, it is recommended to boost with an mRNA-based vaccine as an alternative schedule, even though there are limited data on the safety and efficacy of heterologous prime-boost schedule.[17] This medical development has resulted in the revision of recommendations for the vaccine booster in all patients that have been given a prime dose. It has been recommended to carry on with the boosting by AstraZeneca for the people over the age of 60 years, while a heterologous prime-boost regimen with mRNA vaccine is encouraged for people under the age of 60 years and homologous prime-boost stands as an optional schedule.

3. Immunogenicity and safety of heterologous prime-boost COVID-19 vaccines

Presently, very little data is available on the reactogenicity, immunogenicity, and safety of combining two vaccines from different platforms. In a study conducted by Com-COV (ISRCTN: 69254139, EudraCT: 2020–005085-33) in the UK for the comparison of homologous and heterologous prime-boost vaccines on individuals that were aged above 50 with no known previous comorbidities, the participants were given both AstraZeneca and Pfizer vaccine at 28 and 84 days intervals using heterologous prime-boost regimens and were assessed for the safety and reactogenicity post 7 days of receiving the second dose. The data from this study reported some short-term side effects for both heterologous prime-boost vaccine schedules compared to the homologous prime-boost schedules. However, there have been no differences reported in terms of biochemistry and hematological parameters. The study suggests that younger participants should be included in further studies to evaluate thrombotic thrombocytopenia concerns and other vaccines produced by Moderna and Novavax should also be incorporated in the evaluation protocols.[6] Another study assessed a homologous prime-boost vaccination by giving ChAdOx1 nCoV-19 vaccine (AstraZeneca) for both shots and compared it to a heterologous prime-boost vaccination using ChAdOx1 nCoV-19 for the first dose and mRNA-1273 (Moderna) for the booster dose.[19] This study found that the level of SARS-CoV-2 specific neutralizing IgG development post-ChAdOx1 nCoV-19 boost increased five times after 7–10 days compared to the day of the boost, while the level of neutralizing IgG increased 115 times when using mRNA-1273 boost over the same time. Nevertheless, it has also been found that a boost of mRNA-1273 induces neutralizing antibodies that have potential efficacy against the variant B.1.351 (Beta variant) of SARS-CoV-2, while the neutralizing antibodies elicited by ChAdOx1 nCoV-19 boost are not entirely effective against this variant, such findings being in line with the previously published studies.[20]

In another study, 420 people who received Covishield were given a second dose of Pfizer after 12 weeks. As a result, the people's immunity was found to have increased by 77-folds. Another data came from Canada, where two doses of Covishield were inoculated in one group, two doses of Pfizer in another, and one dose of Covishield, followed by a second dose of Pfizer, in the third group. In this study, it was found that Pfizer after Covishield gave 50–100-fold enhanced immunity. Such mixed regimens would also help to overcome the challenges of a shortfall of particular vaccines and remove hesitancy around vaccines in people's minds that could have genesis in the programmatic 'errors,' especially in settings where multiple COVID-19 vaccines are being used.

4. Implementing the heterologous prime-boost vaccination schedule

Heterologous prime-boost vaccination means the COVID-19 vaccines used in the first and second doses for the immunization are different, e.g. AstraZeneca and Covaxin, respectively, in the first and second doses. Several countries (Vietnam, Italy, Bhutan, Finland, France, Norway, Spain, Sweden, the United Kingdom, and the USA) are using various combinations of the COVID-19 vaccines to achieve mass vaccination for the timely mitigation of the subsequent waves of COVID-19 globally. These countries have implemented the heterologous prime-boost vaccine strategy (mixing of vaccines) after successful trials in their studies; however, some countries (e.g. Bhutan) facing COVID-19 vaccines shortage have also implemented this strategy to overcome the scarcity of the vaccines. For example, in Bhutan, 90% population had received the first dose of AstraZeneca vaccine, and the deadline to administer the second dose after a gap of 12 weeks was scheduled at the end of August 2021;[21] hence looking at the shortage of the COVID-19 vaccines, the Government decided to implement the heterologous prime-boost vaccination. In addition, Bhutan received around 0.55 million doses of AstraZeneca from India under the 'Vaccine Maitri' initiative by the Government of India.[22]

In a recent study conducted by the Indian Council of Medical Research (ICMR), the mixing and matching of Covaxin and Covishield vaccines have shown an apparent better capacity to build immunity against the SARS-CoV-2.[23]

In Denmark, the frontline personnel in the health sector and the elderly received their first injection with the AstraZeneca vaccine and were later vaccinated using Pfizer or Moderna vaccine for a second dose. As per the statement of Denmark's State Serum Institute, the AstraZeneca COVID-19 vaccine was combined with a second dose of either Pfizer-BioNTech or Moderna vaccine that provided "good protection." The study showed that 14 days after a combined vaccination program, the risk of infection with SARS-CoV-2 was reduced by 88% compared to unvaccinated individuals.

Russia's Direct Investment Fund (RDIF) has also clarified that the trials of mixing the first dose of the Sputnik V vaccine with AstraZeneca's shot revealed no serious side effects and no subsequent coronavirus cases among the volunteers. Earlier, the health ministry's ethical committee of Russia suspended the use of such heterologous prime-boost vaccine regimens in May 2021 due to a lack of trial-based data; however, these were approved in July 2021 after successful trials of the Sputnik V vaccine with AstraZeneca. The full results of the trials are to be published soon by the Government of Russia.

5. Conclusion and recommendations

Conclusively, sufficient reliable data are available on the use of heterologous prime-boost vaccination to prove that this process gives enhanced immunity. It is also essential to consider it from the perspective of various countries, which are facing a shortage of COVID-19 vaccines. There is a need for the analysis of the long-term effects of such trials involving heterologous prime-boost vaccine regimens before the widespread implementation in the large population. If the same vaccines are available for the first and second doses for the beneficiaries, there might not be a need to go for the heterologous prime-boost vaccine strategies. However, as the results of the heterologous prime-boost vaccination-based studies have shown excellent and positive effects towards the delta variant, this may serve as a new choice. Therefore, these vaccines should not be made compulsory; however, the choice may be given to the beneficiaries to opt for the heterologous prime-boost immunization.

In conclusion, the heterologous prime-boost vaccination against COVID-19 has been found to be safe as per the various clinical trials conducted in various countries across the globe. Furthermore, combining the two vaccines induces more neutralizing antibodies and could have even more potent efficacy against the emerging variants of SARS-CoV-2. Thus, mixing these COVID-19 vaccines not only enhances the efficacy but might also fulfill the vaccine demands globally by overcoming the vaccine shortage in several countries such as Bhutan.

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Authors' contributions

OPC did the ideation, conceptualization, data curation, writing original draft, reviewing, and editing. PR executed the conceptualization, writing original draft, reviewing, and editing. JQA, TAM, IS, AJRM did the reviewing and editing. All authors critically reviewed and approved the final version of the manuscript.

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