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Heterologous vaccination in the pre COVID and COVID era: An encouraging and promising strategy

[1]Pooja Pandey, Senior Resident, Department of Microbiology, ESIC Medical College & Hospital, Faridabad

[2]Raunak Bir, Assistant Professor, Department of Microbiology, ESIC Medical College & Hospital, Faridabad

[1]Rahul Ranjan, Senior Resident, Department of Microbiology, ESIC Medical College & Hospital, Faridabad

[2]Jayanthi Gunasekaran, Assistant Professor, Department of Microbiology, ESIC Medical College & Hospital, Faridabad

[2]Sanchi Kashyap, Assistant Professor, Department of Microbiology, ESIC Medical College & Hospital, Faridabad

[2]Vishwanath S. Yadav, Assistant Professor, Department of Microbiology, ESIC Medical College & Hospital, Faridabad

[3]Rajiv Mohan Gupta, Professor & Head of the Department, Department of Microbiology, ESIC Medical College & Hospital, Faridabad

[4]Asim Das, Dean, ESIC Medical College & Hospital, Faridabad

[5]Anil K Pandey, Medical Superintendent, ESIC Medical College & Hospital, Faridabad

Corresponding Author: Rajiv M. Gupta, Professor & Head of the Department, Department of Microbiology, ESIC Medical College & Hospital, Faridabad, Haryana.

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Abstract

The emergence of the COVID-19 pandemic in early 2020 has prompted global efforts to develop effective vaccines to curb the spread of the virus. In this context, heterologous vaccination, a strategy involving the administration of different vaccines for prime and boost doses, has garnered increasing interest. However, this concept of utilizing diverse vaccine combinations has its roots in pre-COVID times when it was explored to enhance immune responses against various infectious diseases. We begin by examining the theoretical basis of heterologous vaccination, highlighting its potential to elicit stronger and more durable immune responses compared to homologous vaccination, where the same vaccine is used for both doses. We delve into the underlying immunological mechanisms driving this phenomenon and explore pre-COVID experimental studies that laid the groundwork for understanding its efficacy and safety. In conclusion, heterologous vaccination has emerged as a promising immunization strategy from pre-COVID to the COVID era, offering unique opportunities to optimize immune responses and tackle the challenges presented by the pandemic. However, further investigations are required to fine-tune protocols, ensure safety, and validate its applicability to other infectious diseases, thereby paving the way for a more resilient and effective global vaccination strategy.

Keywords: Heterologous vaccination, homologous vaccination, prime boost, immunity.

Introduction

SARS CoV-2 pandemic wreaked havoc on people globally, and made us to doubt our years of development in the field of medicine and biomedical research. It is urgent that in the future the viral infections be stopped in its early stage; vaccination is the only effective way we have for now.

The existing vaccine supply, however, is insufficient to meet the unprecedented global demand, making it difficult for emerging countries with huge populations to immunize their constantly expanding populations. The only way to stop mitigate increasing morbidity and mortality is with an effective vaccine and its availability globally. WHO states that 183 vaccine candidates are in the clinical development stage and 199 are in the pre-clinical development stage (https://www.who.int/publications/m/item/draft-landscape-of-covid-19 candidate-vaccines) [1]. SARS-CoV-2 mutations has been linked to increased transmissibility and infectiousness. Current scientific research suggests that these mutations have dampening effects on Immunity brought on by vaccination [2-3]. This leads to development in the direction of novel vaccines and the affectivity of the currently used vaccination methods, such as heterologous vaccination. The heterologous vaccination strategy combines different vaccines that have previously been used and have the same antigens. BCG, MMR, and OPV vaccinations have all been used in the past to study the consequences of heterologous immunization. Recently, heterologous prime/boost vaccination against SARS CoV-2 has gained popularity. A separate vaccine should now be given as the second dose to those who have already received any vaccine to prime their immunity. Although there is still information to be addressed on reactogenicity, efficacy, and safety. We want to evaluate the heterologous vaccination approach in this review against the SARS CoV-2 virus and its usage in the pandemic's containment.

Mechanisms of heterologous prime boost vaccination

Recombinant protein vaccines and DNA vaccines produce antigen-specific responses through several ways. DNA vaccines stimulate a powerful cell-mediated immune response that helps to prime memory B cells that are specific to a particular antigen. The booster protein vaccination works by encouraging memory B cells that are specific for an antigen to develop into plasma cells and secrete antibodies [4]. The heterologous prime-boost approaches have the potential to be more successful than the homologous prime-boost approaches regarding certain immunological responses. Comparatively to homologous boosting, this sequential vaccination method using various vectors can induce high levels of CD8+ T-cells and CD4+ T-cells of the Th1 subtype [5]. In heterologous prime boost vaccines strategy, the order of vector administration is the most crucial factor. DNA prime-adenoviral approach compared to reversed adenoviral prime-DNA boost or homologous prime-boost with the identical vaccines, utilizing HCV E2 as a model antigen evoked the highest amount of Th1 CD4+ T cell responses [6]. Two key concepts of efficient DNA prime/virus boost immunization shown in the studies are: (a) significance of DNA vaccines as prime vehicles and attenuated viruses as boosters; and (b) kind of the boosting virus [7]. Other variables may also contribute to the immunogenicity of heterologous prime-boost. For instance, a protein boost after a formulation based on microparticles could increase the effectiveness of DNA vaccine prime [8]. On the other hand, enhancing our comprehension of the fundamental biology of T-cell memory the development of long-term immunological memory using these techniques.

Need for prime boost

The booster regimens have been shown to be successful in eliciting both humoral and cell-mediated immune responses, booster regimens are required [9]. There are two methods for enhancing the immunological response. Firstly, homologous prime-boost technique, in where both priming and boosting regimens employ the same formulation. Secondly, the heterologous prime-boost approach uses various priming and boosting formulations [10] [Fig 1]. According to several earlier investigations, the heterologous prime-boost technique is more effective than the homologous prime-boost strategy [11]. Heterologous prime-boost vaccination has the benefit of generating both humoral and cell-mediated immunity against most of the vaccine's antigens. Recombinant live vector vaccines and DNA vaccines, for instance, induce excellent immune response. A better humoral immune response is primarily elicited by the cell-mediated immunity (CMI) and subunit vaccines [10]. With the same DNA vaccine, it was found that heterologous immunization results in 4- to 10-fold greater T cell responses [12] as compared to homologous prime-boost vaccination. It has been found that protein-based homologous immunization is very effective at eliciting humoral immune responses but less successful at eliciting strong cell-mediated immunity, which is the main form of defence against intracellular infections [13–14]. Recombinant viral vectors or proteins are frequently used as the booster in an efficient prime boost immunization which includes DNA vaccine as the prime.

Pre pandemic heterologous prime/boost vaccination

Hu et al. showed that protection against the disease was provided when Macaca fascicularis were previously inoculated with recombinant vaccinia virus expressing SIV mnegp160 antigen when boosted with gp160 protein generated in baculovirus-infected cells [15]. According to Hu et al., using a live recombinant vaccine as a primer and a subunit recombinant protein as it boosts result in more immunogenicity than using either immunogen alone.

According to Girard et al., greater antibody titers were obtained when a chimpanzee primed with recombinant vaccinia virus was infected with several booster doses of a combination of recombinant HIV-1 proteins or synthetic peptides [16]. According to Sin et al., priming with a DNA vaccination that expresses the herpes simplex gD antigen Significant antibodies and Th1 cytokines were produced in response to the recombinant gD protein and the Herpes Simplex Virus type 2 (HSV-2) [17]. According to Alekseeva et al., either a single dose or administering highly expressed HCV core gene via serial injections reduces the immune response to the core. However, the deleterious consequences of intracellular core expression can be manoeuvred utilizing a heterologous DNA prime/protein boost strategy [4]. In mice and guinea pigs, Chmielewska et al. showed that immunization with the adenovirus vaccine as the primary vaccine and the recombinant HCV E1E2 glycoprotein plus MF59 as the booster vaccine resulted in broad HCV-specific CD8+ and CD4+ T cell responses as well as functional Th1-type IgG responses [18]. Intra-nasal immunization with the DNA prime-VLP boost elicits effective cellular and humoral anti-HIV1 immunity, as shown by Buonaguro et al. The mucosal and systemic immunity cross-clade neutralizing activity was produced after vaccination [19]. When compared to L1 DNA alone, Kianmehr et al. showed that immunization with the L1 DNA/L1 VLP regimen results in greater immunogenicity [20].

In healthy adults who have never had malaria, Dunachie et al. found that a DNA Prime-Modified Vaccinia Virus employed as a prime and an MVA (modified vaccinia

virus Ankara) booster vaccine encoding thrombospondin-related adhesion protein provide moderate protection against Plasmodium falciparum. Previous study shed light on the significance of antigen selection for immune protection by demonstrating that immunity was not evoked by the same combination vaccination when circumsporozoite protein was employed in place of thrombospondin-related adhesion protein [14]. Heterologous immunization has previously been accomplished using a variety of vector-based vaccines. The following are justifications for employing vector-based vaccines in heterologous vaccination: Since Simian adenoviruses often do not infect humans, the bulk of these vectors present themselves as an appealing vaccination platform. It is unclear how common adenovirus 3 (ChAd3) and other simian vectors are in humans. ChAd3 has already undergone evaluation as a potential vaccine candidate for illnesses like hepatitis C and the human immunodeficiency virus. By employing recombinant Bacille Calmette-Guérin (BCG) as a priming agent and an adenovirus 35-vector booster to express a fusion protein made up of Ag85A, Ag85B, and TB104 in rhesus macaques, Magalhaes et al. showed that this procedure elicited a strong immunological response. Another investigation was conducted on calves, and priming was carried out utilizing DNA vaccine made up of Ag85B, MPT64, and MPT83 antigens. stronger immune responses and better protection than BCG were shown by the results [21]. In a mouse study by Sin et al, DNA vaccination was employed as a prime, and recombinant gD protein (gD antigen of herpes simplex virus type 2 [HSV-2]) was utilized to augment the immune response. The results showed better antibody response, T cell proliferation, and Th1 cytokine production. Additionally, vaccination in animals has been shown to be effective when heterologous vaccines have been employed, such as DNA vaccine as a primer, inactivated rabies vaccine as a follow-up, and recombinant PA antigen against anthrax as a booster. The induced immunological response showed increased antibody as an impetus. When compared to homologous prime boost using DNA vaccine or just inactivated influenza vaccine alone, the results showed improved immunogenic response [22].

Reason for development of heterologous prime/ boost vaccination strategies

Currently, 199 vaccine candidates are in pre-clinical development and 183 vaccine candidates are in clinical development. It is crucial to either create next-generation vaccines or streamline the current immunization tactics since the introduction of new variants has impeded the effectiveness of the current emergency vaccinations.

Concerns about the safety of such vaccines have been raised due to the adverse reactions. As previously observed [23, 24], the effectiveness of vector-based vaccinations in people with pre-existing immunity to the viral vector elicits decreased immune responses. Even the use of mRNA vaccine has shown poor immunogenicity of adjuvants [25–26]. Certain vaccines, such as inactivated BBIBP-CorV [27] and recombinant ZF2001 [28], generate relatively short-lived cell-mediated T cell responses. Ad5-vectored vaccine (Can-Sino) is one example of a vector-based vaccine that produces a significant cell-mediated T cell response but very dainty neutralizing antibody (NAb) responses [29]. However, in order to optimize the level of protection provided by vaccination and to make the most use of the resources at our disposal, we must create a new field that will enable us to get superior advantages, such as heterologous vaccination.

SARS CoV-2 heterologous prime/boost vaccination:

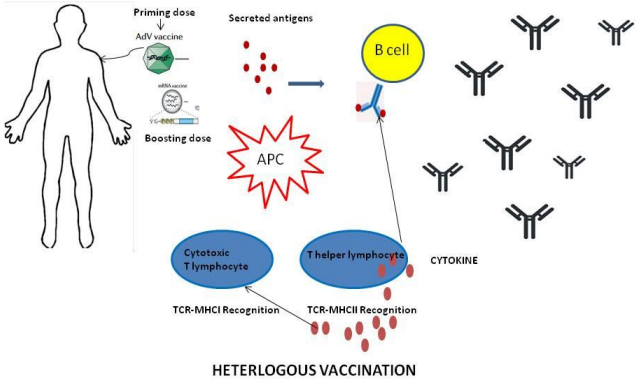
Following vaccination with an adenoviral vectored vaccine (ChAdOx1 nCoV-19/AZD1222) against SARS-CoV-2 and a self-amplifying RNA (saRNA) vaccine, Spencer et al examined the immunological response elicited by heterologous vaccination in mice [30]. The outcomes showed better T cell mediated immune response and greater Neutralizing antibody titres. In a proof-of-concept study by Lin et al two healthy volunteers who had received two doses of the inactivated whole-virus COVID-19 vaccine were administered an mRNA vaccine candidate (LPP-Spike mRNA) after 7 months of the original dosage. The outcomes showed improved responses from memory B cells and T cells [31]. The immunogenicity and reactogenicity of the BNT162b2 booster dose and ChAdOx1-S priming dose were evaluated by Borobia et al. A strong immune response and minimal reactogenicity were brought about by the vaccination. However, there was no homologous vaccine comparator available, making a direct comparison impossible [32]. To study a cohort of 26 individuals, Groß et colleagues employed heterologous ChAdOx1 nCoV-19/BNT162b2 immunization. ChAdOx1 nCoV-19 was used for the priming dose, followed by a BNT162b2, booster 8 weeks after the last dose. Reactive T and B cell immunity was produced. The problematic mutations B.1.1.7, B.1.351, and B.1.617 might be effectively neutralized by vaccine recipients' sera [33]. In clinical trials in China, the value of adopting a heterologous prime-boost technique with the several COVID-19 vaccine candidates was documented. A mouse model was used to test these potential vaccines [34]. The inactivated/recombinant subunit/mRNA vaccine was given as a booster dose after the priming dose of the adenovirus vector vaccine. The findings showed increased neutralizing antibody levels and higher Th1-T cell responses. Shaw et al. showed increased side effect rates, including fever, and increased systemic reactogenicity, in of local or systemic reactogenicity [36]. In accordance with earlier findings in mice, pigs, and non-human primates by Graham et al. and Doremalen et al. [30,37-38], Spencer et al. have demonstrated that heterologous vaccination regimens elicit better antibody responses post-vaccination with good NAb titres after heterologous prime-boost compared to the homologous vaccination with ChAdOx1 nCoV-19.

When compared the homologous arm of Covishield and Covaxin, Rajni et colleagues found that the NAb titer in the vaccinees of the heterologous arm was considerably greater [39]. Alpha, Beta, and Delta Variant of Concern (VOC) were neutralized by the heterologous group's sera. Heterologous arm had greater humoral immune arm IgG titers than homologous arm for S1-RBD, N protein, and inactivated SARS-CoV-2 antigen. Other research has reported similar results. Studies on the cellular immune arm have not revealed any appreciable reaction. When compared to Covaxin vaccination recipients, Covishield vaccine recipients showed increased CD8+ cytotoxic T cell activity.

Conclusion

Today, heterologous prime-boost vaccinations are used as a primary strategy to improve immune responses to a wide range of diseases. Combining the generation of humoral and cell-mediated immunity is heterologous prime-boost immunization. Recombinant viral vectors boost CD4+ and CD8+ T cells, whereas DNA vaccines more effectively promote the humoral and CD4+ T cell response. certain of these Clinical trials for prime-boost immunizations have been conducted, and the outcomes are highly encouraging. We need to get a solid grasp of T-cell biology, vaccine vectors, and vaccination schedule in order to continue developing such techniques. The

solution to containing this pandemic may lie in heterologous vaccination. Heterologous vaccination, however, may be of relevance for several reasons, including logistical and clinical efficacy, when assessing the current situation in a poor nation like India where the epidemic has had terrible effects. It is very challenging to provide a single vaccine to the huge population. Therefore, in such circumstances, heterologous vaccination may show to be of the highest effectiveness. Accepting heterologous vaccination will provide us a chance to improve the vaccination program. The acceptance of heterologous vaccination will present a chance to improve the adaptability of the vaccination program. It would be simpler to manage changes in the supply chain.Better immune responses and increased effectiveness are produced by heterologous regimens. Better techniques and tools need to be developed considering the appearance of novel variations, and heterologous vaccination may prove to be one of those instruments. However, it is crucial to investigate this tactic and demonstrate it to larger cohorts. In conclusion, heterologous vaccination protocols against COVID-19 offer the chance to quicken immunization efforts over the world, maximizing their effect on the pandemic's management.



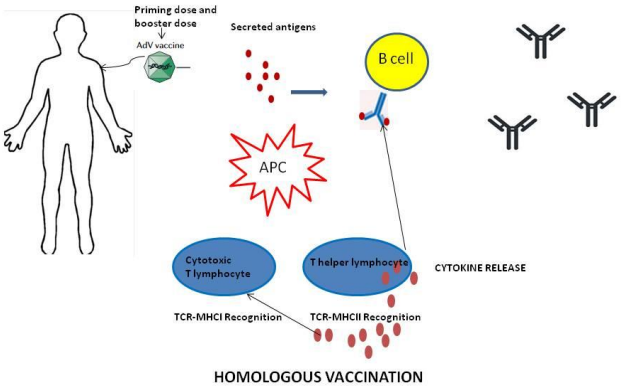


Fig 1: Pictorial representation of Heterologous and Homologous vaccination approaches

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