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Commentary

Heterologous COVID-19 vaccination as a strategy to accelerate mass immunization

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Since the emergence of the COVID-19 pandemic in 2019, several vaccines against SARS-CoV-2 have been developed and implemented worldwide. More than 5 billion individuals have received the first dose of a COVID-19 vaccine. Although some of the COVID-19 vaccines are based on novel technologies such as mRNA platforms, COVID-19 vaccines have been approved for emergency use within an extremely short timespan compared with the normal regulatory processes in vaccine development raising questions about the safety and the long-term durability of the vaccine response.

Despite the unprecedented speed of development and roll out of COVID-19 vaccines, many challenges to mass vaccination remain including vaccine supply, deployment, and uptake and, consequently, vaccination rates are still low in many low- and mid-income countries. Other challenges to mass vaccination include issues with vaccine supply chain disruption and delay, continuous SARS-CoV-2 Spike mutations leading to the development of new variants of concern, waning immunity, and intermittent safety concerns with emergency use authorized vaccines [1,2]. The consequence of all these challenges is a delay in vaccine deployment and, therefore, further optimization of vaccine strategies is of highest importance to global mass immunization against SARS-CoV-2.

Of particular interest and importance is the question of whether different COVID-19 vaccines can be combined and still induce protective antibody responses of the same or higher magnitude than homologous vaccine regimens (e.g. two or more shots of the same vaccine). If so, heterologous COVID-19 vaccination regimens would provide much greater flexibility in both primary vaccination and the administration of booster shots to maintain high levels of protective antibodies in populations. Pereson et al. [3] were the first to report the comparison between immunogenicity and reactogenicity in a sequential prime-boost vaccination with homologous Gam-COVID-Vac (Sputnik V; Gamaleya Research Institute of Epidemiology and Microbiology, Moscow, Russia), an adenoviral vectored vaccine with a heterologous vaccination regimen with Gam-COVID-Vac and mRNA-1273 (Moderna, Cambridge, MA, USA). They conducted an observational cohort study including 190 participants in a real-world setting in Argentina. The inclusion period was between December 2020 and August 2021. The authors reported significantly higher titers of anti-S-RBD (anti-spike protein-receptor-binding domain) immunoglobulin G (IgG) in the heterologous vaccinated group compared with the homologous Gam-COVID-Vac vaccinated group. They did not include an mRNA-1273 homologous vaccinated group in the cohort, and, therefore, it is unknown whether mRNA-1273 entails an additive or synergistic effect in this study. Although the data on the effectiveness of Gam-COVID-Vac in mixed vaccine regimens is sparse, there have been several studies examining the heterologous vaccination regimens that combine an adenoviral vectored vaccine with an mRNA vaccine. A randomised controlled trial by Liu et al. [4] examined the immunogenicity of vaccine regimens including the adenoviral vectored vaccine ChAdOx1 nCoV-19 (AstraZeneca, Cambridge, UK) and the mRNA vaccine BNT-162b2 (Pfizer BioNTech, New York, NY, USA) in different combinations. Liu et al. found that the concentrations of SARS-CoV-2 anti-Spike IgG reached at least the same plasma levels as observed after the homologous ChAdOx1 nCoV-19 vaccination. The results from both Pereson et al. and Liu et al. were in line with several other studies, both randomized controlled trials and observational studies [5–8]. An open-label clinical trial conducted by Atmar et al. examined the efficacy and safety of the

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homologous and heterologous booster vaccinations with either mRNA-1273, Ad26.COV2.S or BNT-162b2 among individuals who already had completed a two-dose vaccination against COVID-19 [9]. They found that all of the booster vaccine regimes were immunogenic, regardless of which primary vaccine regimen the study participants had received. Both binding and neutralizing antibody titers were similar or greater in the heterologous boosted group compared with the homologous group.

Pereson et al. reported an increased reactogenicity in the Gam-COVID-Vac/Moderna group compared with the Gam-COVID-Vac/Gam-COVID-Vac group. This was consistent with the results from previous studies comparing reactogenicity in the heterologous vaccine regimens including the adenovirus vectored vaccines, mRNA vaccines, and to the homologous vaccine regimens consisting of adenoviral vectored vaccines [6,7]. However, overall, both the homologous and the heterologous regimen in the Pereson et al. study were considered to be well tolerated. Further, the authors concluded that the heterologous vaccine regimen might be the best option for individuals with no prior SARS-CoV-2 infection, as the anti-S-RBD IgG were 8-fold higher among individuals with no history of COVID-19 receiving the heterologous vaccine regimen compared with the homologous vaccination regimen.

It is, however, also important to note that the study by Pereson et al. had some limitations that may have impacted the generalisability of the trial results. First, the vaccine regimen subgroups were relatively small, which reduced the power of the study to make definitive conclusions on vaccine effectiveness and safety. For instance, only 13 participants were >60-years-old in the homologous group, and only 9 participants were between 24- and 45-years-old in the heterologous group. Second, due to the observational design, the distribution of vaccines and the resulting vaccination regimens in the different groups were not random as acknowledged by the authors. Healthcare workers were prioritized for vaccination, therefore they were more likely to have received a homologous vaccination scheme with Gam-COVID-Vac. A larger proportion of the >60-year-old individuals received a heterologous vaccination regimen, which have might biased the antibody response in this group to be lower compared with the homologous group. Third, the authors did not report data on comorbidities among the study participants. Comorbidity has been reported in multiple studies to impact vaccine responsiveness and thus a higher frequency of comorbidity in a specific subgroup, such as the older age group, could bias the vaccine response to be lower in the heterologous vaccinated group. In fact, certain comorbidities are associated with SARS-CoV-2 vaccine hyporesponsiveness [10], and elderly individuals generally have a higher burden of comorbidity, which makes adjusting for comorbidity very relevant. Finally, it would be interesting to include measures of cellular immunity against SARS-CoV-2 in comparisons of heterologous and homologous vaccination regimen, as several reports have suggested that T cell mediated immunity is important in preventing progression from mild to severe COVID-19 [11].

The results reported by Pereson et al. were based on data collected before the emergence of the omicron variant, which now is the most dominant SARS-CoV-2 strain globally. Omicron has raised concerns because of its increased transmissibility and ability to evade existing both past infection-induced as well as vaccine-induced SARS-CoV-2 Spike neutralizing antibodies [12]. A study by Garcia-Beltran et al. concluded that mRNA vaccines exhibited potent neutralisation of omicron [13], but this was not found in a study by Pérez-Then et al. [14]. Pérez-Then et al. compared neutralization capacity of Spike-specific antibodies against the SARS-CoV-2 ancestral virus and the delta and omicron variants among individuals receiving a primary vaccine series consisting of a two-dose CoronaVac regimen followed by a booster with BNT-162b2. The authors used a reference consisting of a previous cohort who received two doses of a mRNA vaccine against SARS-CoV-2. The authors found that the omicron variant escaped neutralising antibodies elicited by two mRNA vaccines. The study participants who had received a two-dose regimen with CoronaVac had no detectable plasma IgG neutralization effect against omicron infection *in vitro*. After the participants had received the heterologous booster dose with BNT-162b2, the neutralization activity against omicron increased 1.4-fold compared with the reference group.

Although peak vaccine responses are often used to compare the different vaccination strategies, another important aspect when comparing homologous to heterologous vaccine regimens is the durability of vaccine-induced antibodies. In a large, nonrandomized, parallel group, phase 4 study, including more than 6500 participants, the authors demonstrated that BNT-162b2 was associated with the decreased durability of vaccine-induced antibodies compared with mRNA-1273, both for Spike IgG and Spike-ACE2-receptor antibody [10]. Although this difference in the durability between homologous vaccine regimens could indicate the differences in the antibody responses durability between the homologous and heterologous vaccine regimens, the authors stated that selection bias precluded them from making any strong conclusions about potential vaccine regimen superiority between groups.

Collectively, based on the current body of evidence, it was not possible to conclude that the heterologous vaccination regimens offer superior protection against omicron or other variants of concern compared to homologues vaccine regimens.

Conclusion

There is still a need for COVID-19 vaccine strategies to evolve, not only to provide better protection against infection and severe disease, but also to allow for more flexibility in the global roll out of mass vaccination. Although the study by Pereson et al. is a valuable addition to the rapidly evolving field of COVID-19 vaccines, our understanding of the immunogenicity and reactogenicity of homologous versus heterologous COVID-19 vaccination regimens is still incomplete. A sizable share of the world's population has not had their first or second vaccine dose yet, whereas at the same both third and fourth booster doses are being rolled out in other parts of the world. The pandemic is an ongoing health crisis and flexibility in vaccine schedules is crucial. More research is needed to add critical insights on alternative COVID-19 vaccination regimens that can be used to make informed decisions on the implementation of heterologous vaccination schedules. Further, some of the existing data has also raised the possibility that heterologous vaccination may be preferred in specific populations, such as those who have no previous infection with SARS-CoV-2 at the time of initiating the primary vaccination regimen. Whether such heterologous vaccine regimens truly provide a superior protection should, however, be investigated in future randomized trials. Overall, the current literature has suggested that heterologous vaccine regimens, which include a second or third vaccination shot with a mRNA vaccine, are noninferior to homologous vaccine regimens and therefore could be part of the strategy to accelerate mass immunisation. Further research examining the durability of other vaccine regimens and vaccine protection against new variants of concern remains of highest importance.

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