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REVIEW

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COVID-19 vaccines mix-and-match: The concept, the efficacy and the doubts

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Abstract

The search for developing effective vaccines against SARS-CoV-2 began with the start of the COVID-19 pandemic, and the first vaccine dose was administered in December 2020. Today, full vaccination of most of the world's population is considered the most important means to overcome the COVID-19 pandemic. Vaccination has been associated with various struggles. Some adverse reactions have resulted in the discontinuation of the specific vaccines use in some countries. Countries in poor regions have faced difficulties supplying enough vaccine doses, and the emergence of new variants of concern has resulted in reduced effectiveness of available vaccines against COVID-19. The mix-and-match strategy, using heterologous vaccines in the first and second doses, might successfully solve the mentioned struggles. Moreover, this strategy has been associated with higher cellular and humoral immune responses without significantly increasing the adverse reactions. Hence, this strategy can help improve the vaccines' effectiveness, and act as a solution for vaccine shortage in poor regions.

KEYWORDS

COVID-19, mix-and-match, SARS-CoV-2, vaccination, vaccine

1 | INTRODUCTION

Research for developing effective vaccines against SARS-CoV-2 began as the COVID-19 pandemic started with a hope to put an end to it, and the first vaccine dose was administered in December 2020. To date, more than three billion people have received at least one dose of the available COVID-19 vaccines and about two billion people are fully vaccinated worldwide, which accounts for roughly 27% of the world's population.[1,2] AstraZeneca vaccine is the most used vaccine worldwide, administered in 182 countries, followed by Pfizer—BioNTech, Moderna, and Sinopharm vaccine, administered in 115, 68, and 66 countries, respectively.

In March 2021, the use of AstraZeneca vaccine was prohibited in young women in Germany with the fear of escalated thrombolytic events, and those to whom this vaccine was administered as the first dose had to get an alternative vaccine for the second dose.[3,4] Ever since many countries including France, Denmark, Italy, Canada, USA, Bahrain, South Chorea, Spain,

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Finland, Sweden, United Arab Emirates, and Norway have been mixing COVID-19 vaccines.[5]

Available data from Centers for Disease Control and Prevention (CDC) shows that vaccination is not distributed equally throughout the world and poorer nations are facing a lot of struggle to keep up with the vaccination program.[1,6] Furthermore, mutations in the genome of SARS-CoV-2 and the emergence of new Variants of Concern (VOC), have resulted in reduced effectiveness of the available vaccines.[7]

Previous studies on using heterologous vaccines in prime-boost immunization strategy have shown great success. Studies suggest that by evoking both cellular and humoral immune response, heterologous vaccines can result in 4–10 times higher T-cell responses.[8]

Scientist are now convinced, that the mix-and-match approach can both solve the problem of vaccine shortage in poorer regions, and evoke greater immune response in the recipients. Hence, many countries have started mixing COVID-19 vaccine doses, using both the vaccines of the same platform for both doses or administering each dose with a vaccine of a different platform.[5,7]

2 | AVAILABLE VACCINES AGAINST COVID-19

Several vaccines are currently available in various countries to protect against COVID-19 infection. These vaccines are available on different platforms. A group of these vaccines contains nucleoside-modified messenger RNA (modRNA), from which we can name BNT162b2, developed by Pfizer/Biontech, a lipid nanoparticle formulation, nucleoside-modified messenger RNA (mRNA) that encodes full-length spike on the surface of the SARS-CoV-2 mutated form in the prefusion conformation,[9–11] and mRNA-1273, developed by Moderna, also a lipid-nanoparticle, which encodes prefusion-stabilized spike glycoprotein.[12]

Another platform on which COVID-19 vaccines are made, is through the use of vectors, such as ChAdOx1 nCoV-19 or AstraZeneca vaccine (AZD1222), developed by Oxford University, a replication-deficient chimpanzee adenoviral vector, which contains the SARS-CoV-2 structural surface glycoprotein antigen gene,[13–16] Gam-COVID-Vac vaccine (Sputnik V), a heterologous recombinant adenovirus (rAd)-based vaccine which carries the gene for SARS-CoV-2 full-length glycoprotein S (rAd26-S and rAd5-S),[17] and Ad26.COV2.S, developed by Johnson & Johnson, a recombinant and replication-incompetent adenovirus serotype 26 (Ad26) vector which encodes a full-length and also stabilized SARS-CoV-2 spike protein.[18]

Another group of COVID-19 vaccines is protein subunit vaccine such as NVX-CoV2373, a nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant.[19]

A conventional method by which COVID-19 vaccines are made, is the use of inactivated virus, from which we can name CoronaVac developed by Sinovac Life Sciences.[20,21]

An overview of the current available vaccines with a finalized status of assessment according to WHO, the platform on which they are made and their probable side effects is summarized in Table 1.

TABLE 1 Available vaccines against COVID-19

Manufacturer	Name of Vaccine	Platform	Efficacy	Adverse effect
Pfizer/Biontech	BNT162b2	Nucleoside-modified mRNA (modRNA)[10]	95%[9]	Pain at the injection site, fatigue, headache, fever[9]
Moderna	mRNA-1273	Nucleoside-modified mRNA (modRNA)[12]	94.1%[12]	Pain, erythema, induration, tenderness, hypersensitivity reactions[12]
Oxford-AstraZeneca	AZD1222(ChAdOx1_nCoV19)	Adenovirus recombinant vector[13,15]	76% (day 22 to day 90 after vaccination)[16]	Fatigue, headache, muscle ache, malaise, chills, feeling feverish, fever[15]
Johnson and Johnson	Ad26.COV2.S	Adenovirus recombinant vector (Ad26)[18]		Fatigue, headache, myalgia, fever, injection site pain[18]
Sinovac, Sinopharm	COVID-19 Vaccine (Vero Cell), Inactivated/CoronaVac	Inactivated SARS-CoV-2 (vero cells)[20,21]	83.5%[21]	Injection site pain, erythema, paresthesia, redness, swelling, allergic reaction, cough, fever, fatigue, myalgia, chill, nausea[20,21]
Gam-COVID-Vac	Sputnik V	Adenovirus vector (recombinant Ad5 and Ad26)[17]	91.6%[17]	Flu-like illness, injection site reactions, headache, asthenia[17]
Novavax	NVX-CoV2373/Covovax	Recombinant spike glycoprotein nanoparticle vaccine (NVX-CoV2373)[19]		injection site reaction, pain, tenderness, erythema, swelling, fever, headache, fatigue, malaise, myalgia, arthralgia, nausea or vomiting[19]

TABLE 2 Studies related to COVID-19 vaccine mixing (Oxford AstraZeneca and Pfizer BioNTech)

Study authors	Number of cases	Type of study	Type of vaccines	Efficacy and duration	Adverse effects
Borobia et al.[27]	*n* = 663	Randomized, phaseII clinical trial	Trial arm:Prime: Oxford AstraZenecaBoost: Pfizer BioNTechControl arm: only received one dose	Trial arm: 150 times greater antibody after 14 days of the second dose, the cellular immune response was quadrupledControl arm: after 14 days, antibody titers were the same as baseline	68.3% of side effects were mild, and 29.9% were moderate; it was also the same in both groups. The most common adverse effects were headache (44%), malaise (41%), chills (25%), mild nausea (11%), mild cough (7%), and fever (2.5%)
Groß et al.[32]	*n* = 26	Prospective, observational study	First dose: Oxford AstraZenecaSecond dose: Pfizer BioNTechNo control group	Sturdy neutralization antibody after two weeks post-Oxford AstraZeneca- activity response against predominant strain with heterologous prime was 3.9 higher than homologous Pfizer BioNTech vaccination—$CD4^+$ and $CD8^+$ T cells reaction happened against SARS-CoV-2 spike peptide after 2 weeks of complete vaccination	The adverse effects of the primary and secondary dose were mild to moderate symptoms (88.4% and 80.8%, respectively)
Shaw et al.[33]	*n* = 830	Single-blind, randomized, phaseII clinical trial	Trial arm: Arm 1: Prime: Oxford AstraZenecaBoost: Pfizer-BioNTechArm 2: Prime: Pfizer-BioNTechBoost: Oxford AstraZenecaControl arm: homologousschedulesArm 1: Prime and boost: Pfizer BioNTechArm 2: Prime and boost: Oxford AstraZeneca	No report yet	Major response against immune system response in heterologous prime-boost compared with other homologous counterparts the most common symptom was fever most of the reaction was observed 48 h after immunization
Hillus et al.[28]	*n* = 340	Prospective, observational cohort study	Arm 1: Prime: Oxford AstraZenecaBoost: Pfizer BioNTechArm 2:Homologous: Pfizer BioNTech	After both homologous and heterologous boost serum antibody was strongly increased- after 3 weeks post-boost immunization: homologous Pfizer BioNTech (99.01%) heterologous Oxford AstraZeneca/Pfizer BioNTech (100.00%)- S1-Ig Gavidity: was higher after heterologous Oxford AstraZeneca/Pfizer BioNTech boost compared with homologous Pfizer BioNTech boost- T-cell reactivity was remarkably higher after heterologous boost compared with homologous boost	The local reaction was a little higher after heterologous booster in comparison with homologous booster-systemic reaction was a much higher primary dose of oxford AstraZeneca (86%) and less frequent after homologous of Pfizer BioNTech(65%)or heterologous oxford AstraZeneca/Pfizer BioNTech (48%) The duration of arm 1 between 2 doses was 10–12 weeks The duration of arm 2 was 3 weeks

3 | RECENT REPORTS OF COVID-19 VACCINES MIXING

Since the outbreak of the Delta variant of the coronavirus, dozens of countries are mixing vaccines, aiming to increase its effectiveness and protection.[22]

There have been successful attempts of mixing COVID-19 vaccines in animals. In one study, the use of Sputnik V vaccine as the first dose and AstraZeneca as the second dose in mice showed that not only did this mixture not cause any particular problem, but it also resulted in higher immunity.[23]

In another study in mice, the effect of using self-amplifying RNA vaccine (saRNA) and adenovirus carrier vaccine (ChAdOx1 nCoV-19/AZD1222) was investigated. The results of this study indicated that the antibody response in the use of these two types of vaccines is higher than using one type of vaccine for both doses.[24]

After these successful animal studies, clinical trials began, mixing COVID-19 vaccines in human populations. Recent studies have shown that mixing the Oxford–AstraZeneca and the Pfizer–BioNTech vaccine triggers an immune response similar to or even more significant than two doses of either vaccines.[25–28] A study showed, that in people who received a dose of AstraZeneca vaccine who were injected with the second dose of Pfizer, the immunoglobulin G (IgG) and IgA anti-spike (S) response was 11.5 times higher than those receiving both doses of AstraZeneca, and the humoral immune response was also better.[29]

In another study, it was observed that in people who received the first dose of ChAdOx1 nCoV-19 vaccine and used mRNA vaccine (BNT162b2 or mRNA-1273) for the second dose, the spike-specific IgG, neutralizing antibodies, spike-specific CD4 T cells, spike-specific CD8 T-cell levels and humoral and cellular immune responses was significantly increased.[30]

A second trial phase of a Spanish study demonstrated that mixed vaccination with Oxford AstraZeneca as the first dose and Pfizer BioNTech as the second dose increased antibody levels 150 times more after 14 days of the second dose compared with a control group that received only the first dose.[27]

Com-COV trial with more than 800 volunteers from oxford university demonstrated that mixing Oxford AstraZeneca and Pfizer BioNTech induced a much more strong immune response.[31]

Mix and match trials have not been reported severe side effects yet; a study in Spain shows that 448 people injected Oxford-AstraZeneca for the first dose, then Pfizer-BioNTech for the second dose; they had poor side effects; blood tests show coarse antibody response after two weak from the second shot.[25] Likewise, Charité, Saarland, and CombiVacS showed the same result, side effects of these vaccines were not worse than two shots of the same vaccine. Nevertheless, the Com-COV study demonstrates that mixing vaccines could cause more side effects than prescribing two doses of the same vaccines.[26]

Recent reports of COVID-19 vaccines mixing have been summarized in Table 2 and 3.

TABLE 3 Studies related to COVID-19 vaccine mixing (other vaccines)

Study name	Number of cases	Type of study	Type of vaccines	Efficacy and duration	Adverse effects
Singh et al.[34]	$n = 552$	Cross-sectional study	First dose: Covishield (Oxford Astrezaneca) Second dose: Covaxin	The response of the vaccines and IQR between 21 days or more to 6 months after the second dose showed that anti spike antibody was obviously higher in covishield in comparison with covaxin	Covishield participants had more adverse events compared with Covaxin
Kant et al.[35]	$n = 18$	Clinical Trial	First dose: Covishield (Oxford Astrezaneca) Second dose: Covaxin	Higher IgG and neutralizing antibody in heterologous group compared with homologous group	Lower or similar adverse events

4 | UNDERLYING MECHANISM

Mixing vaccines and using vaccines of different platforms as the second or booster dose has long been practiced before the emergence of SARS-CoV-2. Various methods have been employed using different vaccine formulations in subsequent vaccine doses, and promising results have been achieved. So far, mixing DNA and vector vaccines has been accompanied by higher immunity both in animal models and humans.[36] This method has been used for HPV, HIV, influenza, Ebola, and also trials of HCV vaccines.[36–39] Furthermore, mixing DNA vaccines with protein vaccines in trials of HSV, HIV, and HCV vaccines, mixing of protein and viral vaccines, and also virus-like particle vaccines with DNA vaccines have all been accompanied by higher immune responses.[40,41]

A number of possible mechanisms have been suggested for the higher immunity caused by the use of heterologous vaccines. It is recommended that by using dissimilar vaccine formulations, different arms of the immune system are evoked. Therefore, a combination of cellular and humoral immunity, as an instance, can result in higher and more prolonged immunity. It has also been seen that higher IgG levels, or neutralizing antibodies can be achieved using heterologous vaccines as these vaccines can evoke humoral immunity through different ways.[8]

The underlying mechanism for higher immunity when mixing COVID-19 vaccines has not been clearly described. However, based on the results from available studies on incorporating COVID-19 vaccines, it is indicated that IgG antibodies, neutralizing antibodies, and also cellular immune response are significantly increased using heterologous COVID-19 vaccines compared to the homologous strategy.[27,30,42] This suggests that the same mechanism, long known for other heterologous vaccines, can also be the underlying mechanism for the higher immune response achieved from mixing COVID-19 vaccines.

5 | CONCLUSION

Shortage of vaccines, especially in poor regions, the emergence of new variants of concern that have been partially resistant to available vaccines, and a number of adverse reactions have forced several countries to mix the COVID-19 vaccines.[1,7] This strategy has been associated with significant success. Studies have shown that mixing vaccines of different platforms can result in higher IgG and neutralizing antibodies as well as more strong cellular immune response.[27,30,42] Furthermore, using heterologous COVID-19 vaccines has resulted in higher neutralizing antibody levels against the VOC compared to the homologous vaccines.[42] As a result, both developing and industrialized countries have started taking the mix-and-match strategy into practice with the hope to immunize a greater percentage of their populations effectively against COVID-19.[5]

Studies and trials on mixing the available COVID-19 have been promising as they have been associated with a higher immune response without a significant increase in adverse reactions. Hence, this strategy can help improve the vaccines' effectiveness, as well as acting as a solution for vaccine shortage in poor regions.

AUTHOR CONTRIBUTIONS

All the authors had substantial contributions to the conception of the work. Drafting of the work was done by all the authors. All approved the final draft and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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