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Booster Dose for Tackling Emerging Variant of SARS-CoV-2

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ABSTRACT: A novel species of coronavirus has engulfed the entire world. Its severity and rate at which it transmits have left no country untouched. Massive replication has brought mutation in the genomic sequence of the virus. Due to this, many newer variants of SARS-COV-2 have come into play. Many therapies are available for covid 19, such as Remdesivir, Baricitinib, Molnupiravir, etc., but none are effective at preventing SARS-CoV-2 infection. Even most of the efficacious vaccines against the earlier variants are now inefficacious against, the newer variants. So, the people already vaccinated with the primary course of vaccination are at risk of reinfection and symptomatic COVID 19 illness. Furthermore, the initial immune response produced by these vaccines may have diminished with time, paving the pathway for discussion on the absolute need for time off and booster doses for vaccinated people. Some developed countries like the U.K and Israel favor the booster dose strategy, while some defy it, claiming it is necessary to vaccinate unvaccinated people first rather than giving vaccines multiple times. In this article, we have explained the necessity of booster doses in tackling newer variants. However, for the time being, devising a variant-specific vaccine seems promising to hiatus this transmission.

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INTRODUCTION

A respiratory syndrome came into the voyage on December 31, 2019, in Hubei province, China (1). Initially, the pathogen was unidentified, and the disease was contemplated as "pneumonia of unknown etiology." Soon afterward, a novel coronavirus (CoV) family was associated with the etiology of the illness (2). The four primary coronavirus subdivisions are alpha, beta, gamma, and delta. Alpha coronavirus and Beta coronavirus cause sickness in humans, while Gamma and Delta coronavirus mainly afflict birds (3). Around seven varieties of human CoV cause illness in humans. They are divided into common human coronavirus 229E (HCoV-229E), human coronavirus NL63 (HCoV-NL63), human corona OC43 (HCoV-OC43), and coronavirus HKU1 (CoV-HKU1) (beta CoVs of A lineage). These viruses generally infect the lower respiratory tract in the elderly or immune-compromised people, but people with high immunity only get a mild upper respiratory infection or common cold. The second type is other human CoVs: the Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) (beta CoVs of the B and C lineages). These variants are severely infectious and capable of occurring in epidemics with respiratory-related illnesses of varying clinical seriousness. World Health Organization (WHO) designated the newly identified CoV as covid-19 on February 11, 2020. Through inspection, the International Committee on Taxonomy of Viruses (ICTV) found a significant similarity between the Covid-19 virus and the past SARS-CoVs. As a result, ICTV experts named the virus the SARS-CoV-2 virus. Despite extreme lockdown and isolation measures, the disease has spread worldwide. They are considering the transmissibility and infectivity of the range of the virus; on March 11, 2020, WHO declared the COVID-19 breakout as a global pandemic. The pandemic has affected more than 200 countries worldwide. As of May 2020, 517 million cases of COVID-19 have been reported throughout the world, 472 million are fully recovered, and over 6.2 million deaths have occurred due to COVID-19. Supportive and preventive measures are currently achieved by immunizing patients through vaccination. However, the virus's rapid changes in structure, mechanism, and spread mutation obstruct

the entire vaccination process (4,5). There are lacunae of good review articles showcasing both sides (positive and negative impact) of booster dosing strategy and what are the other possible solutions to tackle newer variants of coronavirus. This article suffices the lacunae by including both the pros and cons of booster dosing strategy along with effective solutions to tackle newer variants. This article serves all the curious readers and learners with the knowledge of coronavirus, its variants, and the effectiveness of the booster dosing strategy. The table in the article includes valuable information on therapeutics for covid-19 and various vaccines under emergency use against SARS-CoV-2.

The limitations of the study: The discussion in section 4 is in consideration of the overall variant not only on one specific variant like omicron, delta, etc.

Inclusion criteria: (1) Articles that are in the English language. (2) Articles on approved vaccines and booster doses. (3) Articles with proper results and findings. (4) Articles published since 2019.

Exclusion criteria: (1) Articles other than the English language. (2) Articles with no extractable data or proper findings. (3) Articles published before 2019.

VARIANTS AND MUTATION OF SARS-COV-2

Ribonucleic acid (RNA) viruses have the nature of undergoing genetic evaluation. Being an RNA virus, the same is happening in the case of SARS-CoV-2 naturally undergoes genetic evaluation, and the same is happening in the case of SARS-CoV-2 (6). As an RNA virus, it mutates itself with time, primarily while infecting a new host, and the resultant variants have distinct characteristics from parent strains. At the initial phase of the pandemic, mutation of the virus was minimal, and D614G was the dominant variant globally because of its speedy transmission (7). But after that, several SARS-CoV-2 were identified: on account of their capacity to increase virulence, nullifying the immunity obtained through vaccination or natural infection, the capability of remaining undetected, or reducing the therapeutic effectiveness of vaccination or medicines (**Figure 1**) (8,9). In considering the unstoppable emergence of different SARS-CoV-2 variants, the Centers for Disease Control and Prevention (CDC) and WHO have devised a classification system for separating the newer variants into Variants of Concern (VOCs) and Variants of Interest (VOIs). The different VOCs are from the (Alpha B.1.1.7 lineage), which was first reported in the UK in September 2020. Through sequencing, 17 mutations were identified in B.1.1.7 (GRY/Alpha Variant). There are eight mutations (N501Y, A570D, T716I, etc.) among 17 mutations which has an enhanced affinity towards the Angiotensin-converting enzyme 2 (ACE-2) receptor that facilitates viral attachment and ensures entry into the cells. The second VOC is Beta (B.1.351 lineage), first detected in South Africa following the 2nd wave in September 2020. It has nine mutations in the spike proteins. Three of them (K417N, E484K, and N501Y) are located in the RBD (Receptor Binding Domain) that assists in binding with ACE-receptors. This highly transmissible variant reduces neutralization via monoclonal antibody therapy post-vaccination and convalescent sera. The third VOC is Gamma (P.1 lineage), first identified in Brazil in December 2020. This B.1.1.28 variant has gathered ten mutations, among which L18F, K417N, and E484K are the three mutations in the RBD and have similar effects to the B.1.351 variant. Fourth is Delta (B.1.617.2 lineage), first identified in India in December 2020, which caused a dangerous second wave in April 2021 in India. It has ten mutations. The Delta variant also affected the US badly. At first, the delta was counted as VOI, but after observing its rapid spread worldwide, WHO put it as VOC in March 2021. The fifth VOC is Omicron (B.1.1.529 lineage), first identified in South Africa in November 2021. Omicron has changed more than 30 spike proteins and infected many people in South Africa, due to which B.1.1.529 was named a VOC. Omicron increases the virulence by 13 folds and is also 2.8 times more infectious than the Delta variant (10). Omicron spike mutations include K417N and E484A (9,11,12). They cause disruptive effects that make Omicron less responsive to the vaccines. And SARS-CoV-2 variants of interest (VOIs) have specific genetic characteristics or changes linked to rapid transmissibility, reduced neutralization through antibodies acquired through frequent infection or vaccination, and the ability to go undetected suppress the efficacy of vaccines. Till now, WHO has detected eight variants of interest (VOIs) called Theta (P.3); Zeta (P.2); Eta (B.1.525); Kappa (B.1.617.1); Lambda (C.37); Epsilon (B.1.427 and B.1.429) and Mu (B.1.621) (3)(52).

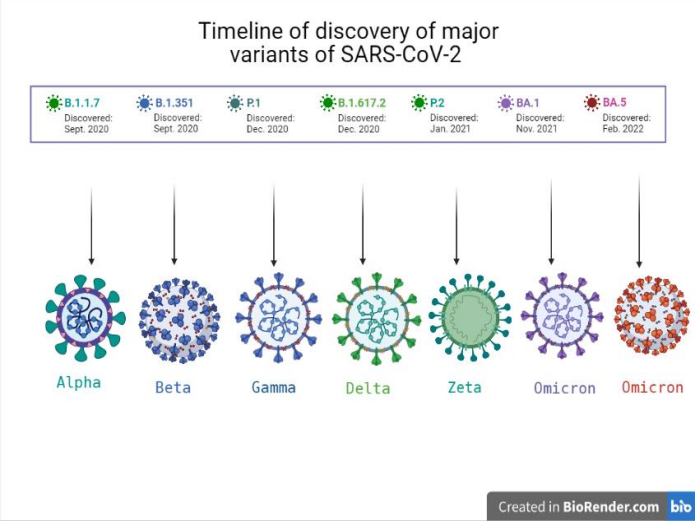

Figure 1: Timeline of discovery of major variants of SARS-CoV-2 (13)

THERAPEUTICS

Covid-19 therapies are split into two categories. 1. Enteral system (oral route; **Table 1**) 2. parenteral system (vaccination; table 2). Various oral drugs are available to treat COVID and post-COVID circumstances, but the disease is becoming more contagious due to ongoing mutations in the RBS (receptor-binding site). All the drugs listed below are used for symptomatic therapy, except Remdesivir. It is the only drug that is proven to suppress the RNA replication of COVID-19

and is strongly recommended by the WHO (World Health Organisation) to treat all stages (both moderate and severe cases) of COVID-19 patients (14). In addition, Baricitinib (a Janus kinase inhibitor) is strongly advisable for harsh or critical COVID-19 patients, and drugs like Sotrovimab, Casirivimab, Imdevimab, Nirmatrelvir, and Ritonavir are advised for use in mild or moderate COVID-19 patients who are at high risk of hospitalization, according to WHO (11,15,16). It's also been suggested that combining Remdesivir with Molnupiravir could improve effectiveness, especially in more severe cases (17). However, for long-term immunity, the WHO strongly recommends vaccinations with one or two booster shots (**Table:1 and 2**). For adults over 50 years old and young persons with a weaker immune system, the Centers for Disease Control and Prevention (CDC) recommends two booster shots vaccines. The first booster dose is given three to four months after the second vaccine, and the double booster dose is given five months later. Other approaches, such as an intranasal vaccine for Covid-19, are in various human trials and have been proven to elicit significant neutralizing antibody production, mucosal IgA, and T cell responses (8). There are a variety of herbal formulations on the market as well, but none of them have substantial proof of combating COVID-19 (18).

Table 1: Therapeutics for COVID-19

Category	Drug name	Route of administration	Application	Reference
RNA-dependent RNA Polymerase inhibitors	Remdesivir	Intravenous	Engages with adenosine-triphosphate to suppress viral RNA synthesis by blocking RNA-dependent RNA polymerases (RdRps).	(19,20)
	Favipiravir	Oral	suppress viral RNA synthesis by blocking RNA-dependent RNA polymerases (RdRps).	(21)
	Ribavirin	Oral (inhalation)	It interferes with mRNA by blocking viral synthesis and mRNA capping.	(22)
	Sofosbuvir	Oral	Sofosbuvir is a prodrug that is converted to the potent antiviral molecule 20-deoxy-20-fluoro-C-methyluridine-50-triphosphate in the liver.	(23)
	Molnupiravir	Oral	It's a prodrug of ß-D-N4-hydroxycytidine which also suppress viral RNA synthesis.	(17)
Viral Protease Inhibitors	Lopinavir/Ritonavir	Oral	Binds with Mpro (coronavirus replication enzyme) and blocks it.	(22)
	Atazanavir	Oral	It prevents from infectious virions by forming an inhibitor enzyme complex.	(24)
Viral entry inhibitors	Hydroxychloroquine phosphate	Oral	ACE2 cellular receptors acidify the endothelial layers and participate in immunomodulation of cytokine release by impeding viral enzymes or activities.	(25)
	Ivermectin	Oral	blocks the association of the SARS-CoV-2S protein with the human ACE2 receptor.	(15)

Category	Drug name	Route of administration	Application	Reference
Monoclonal antibodies	Sarilumab	Subcutaneous	Stops the attachment of IL-6 to IL-6 receptors.	(26)
	Tocilizumab	Intravenous		
Nutritional supplements	Vitamin C	Oral	Immunomodulator and maintenance of tissue barriers in the human body.	(27)
	Vitamin D	Oral		
	Folic acid	Oral		
	Zinc	Oral		
	Corticosteroids	Oral	Reduces mortality in covid-19-treated hospitalized patients who needed supplementary oxygen.	(15)
	Convalescent plasma Therapy	Intravenous (infusion)	Consists of antibodies against SARS-COV-2.	(19–21)
	Azithromycin	Oral	works by attaching with 50S ribosomal subunit of microbes.	
	Baricitinib	Oral	It impedes the signaling mechanism related to cytokine storms which ultimately stops Janus kinases enzyme (JAK 1 & JAK 2).	
	Colchicine	Oral	Mainly blocks the entrance and regeneration of SARS-CoV-2 by inhibiting the polymerization process of the microtubule.	

Table 2: Vaccines under emergency use against SARS-CoV-2 (8,11,16,28)**.**

Name of Vaccine	Manufacturer	Dose	Recommended Booster dose
BNT162b2/COMIRNATY Tozinameran (INN)	BioNTech Manufacturing GmbH	2	Yes (2 boosters)
AZD1222 Vaxzevria, Covishield	AstraZeneca, Serum Institute of India Pvt. Ltd	2	Yes (1 booster; not recommended for 5-11 years children)
Ad26.COV2.S	Janssen–Cilag International NV	1	Yes (2 boosters)
mRNA-1273	Moderna Biotech		Yes (2 boosters)
SARS-CoV-2 Vaccine (Vero Cell), Inactivated (lnCoV)	Sinopharm / BIBP1	2	Yes (1 booster)

COVID-19 Vaccine (Vero Cell), Inactivated/ CoronavacTM	Sinovac Life Sciences Co., Ltd.	2	Yes (1 booster)
Inactivated (Vero Cell)/ COVAXIN	Bharat Biotech, India and Serum Institute of India Pvt. Ltd	2	Yes (1 booster)
NVX-CoV2373/Nuvaxovid	Novavax, Inc.	2	Yes (1 booster)
Sputnik V	Russian Direct Investment fund	2	Yes

STRATEGY FOR BOOSTER DOSE

Within a year after discovering that SARS-CoV-2 is the causative agent of COVID-19, several safe and effective vaccines were licensed worldwide (29). However, even after mass immunization with the main course of vaccination, we have experienced many COVID waves, raising concerns about the durability of immunity generated by these vaccines against the major variants of SARS-COV-2. The alarming rise in COVID infection, hospitalization, and mortality has cleared the way for discussion on the absolute need for, and best scheduling of, booster doses for vaccinated patients. According to Melanie Swift (co-chair of the Mayo Clinic COVID-19 Vaccine Allocation and Distribution Work Group), a booster dosage is designed to serve as a reminder to your immune system (30). The primary vaccination series is intended to elicit an initial immunological response; nevertheless, this initial immune response may diminish with time, necessitating booster vaccine doses.

In the Comparing COVID-19 Booster Vaccinations (COV-BOOST) trial, which was conducted in the United Kingdom to assess the efficacy of COVID-19 booster vaccines against COVID-19-related symptoms, hospitalization, and death, it was discovered that mRNA vaccine, when given as a booster dose, provides a higher booster effect with low reactogenicity regardless of the vaccine used in the primary course of vaccination (12,18,31–36). They observed a significant improvement in protection against symptomatic COVID 19 illness attributable to delta variants following a booster dose of mRNA vaccine, with only a slight fading of immunity after ten or more weeks of immunization. With a single shot of BNT162b2 as a booster dosage, a very high degree of protection (97%-99%) was demonstrated against hospitalization or death, with no evidence of immunity decreasing for up to 9 weeks (37). According to the UK Health Security Agency, a booster dosage can give (70-75)% efficiency against the omicron variety (38). Researchers in Israel, the first nation to use a booster dosage method, discovered that taking a third dose of Pfizer vaccine at least 12 days later reduces the likelihood of infection, and severe sickness, compared to individuals who simply took two doses (39).

Some, in defiance of the booster dosage technique, argue that it is vital to vaccinate unvaccinated people first rather than providing the third dosage to vaccinated people since doing so reduces the probability of replication and mutation in the virus's spike protein, which is the principal source of vaccine ineffectiveness. However, although the benefits of the primary course of the vaccine outweigh the risks, there is a risk if a booster dose is given too soon or too frequently with a vaccine that can cause immune-mediated side effects (e.g., myocarditis in the mRNA vaccine or Guillian Barre syndrome in the adenovirus-based vaccine) (40,41). Moreover, the vaccination containing the antigen from the earlier period of the pandemic is still effective in preventing severe illness from all main variants, showing that these variants have not yet evolved to the point where they may escape the vaccine's memory immune response (42,43).

In this journey of booster dosing strategy, nasal vaccine is also seen as a potential competitor to be a booster shot. Even though many of the approved injectable vaccines against SARS-CoV-2 can prevent the serious illness caused by the coronavirus and its variants, they cannot ward off the infection completely (44). So to block the infection completely, scientists are trying to develop nasal preparations which can prevent the viral entry from the site where the virus makes first contact: The nose, mouth, and throat. Nasal preparation is easy to administer and can provide both humoral as well as mucosal immunity which is hardly seen in the approved conventional injectable vaccines. With no need for syringes or needles for administration, it can reach a lot more people easily however many scientists think, “efficacy is going to be the deciding factor in the battle between nasal vaccines and injectable vaccines” (45).

The choice of a booster technique typically depends on how long immunizations continue to produce an immunological response (46). The booster dose is then satiated, depending on the period. Pfizer's vaccine demonstrates 84 percent efficacy at four months, while Moderna demonstrates 90 percent efficacy at six months. Thus, the recommended intervals between booster doses for the Pfizer and Moderna vaccines are 4 and 6 months (47). However, it has also been noted that individuals over the age of 65 exhibits a diminished capacity for immune response compared to healthy adult individuals. Therefore, taking the severity and fluctuations of a condition into consideration, several booster doses may also be considered as well (48). In Taizhou, China, 1576 participants participated in a study to determine their willingness to receive a booster

dose. Eighty-nine percent of those over 40 years and 92 percent of those under 40 years agreed to have a shot (49). However, it should also be considered that mass immunization should take precedence over booster dose. Future research should consider all study methodologies to create more effective vaccines and give longer sustainability in the event of immunological reactions(50).

CONCLUSION

An extensive booster dose strategy is an effective way of providing prevention from disease and illness associated with different variants of SARS-COV-2, but this should be made mandatory only if there is relevant evidence that it is appropriate. It is preferable to provide a booster injection to a specific population (immunocompromised or older population) (51). Instead of getting a booster dose with the same vaccine, it is preferable to develop a variant-specific vaccine. A similar method is implemented for the influenza virus vaccine.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could appear to influence the work reported in this paper.

DATA AVAILABILITY

Not applicable

AUTHOR'S CONTRIBUTION

Amit kumar has prepared the plot of the manuscript and written the first draft of the manuscript along with Anup kumar, Rittwika Banerjee, and Nayan Das. Later Anup kumar and Rittwika Banerjee revised the manuscript. Nayan Das and Amit kumar critically revised the manuscript. All the authors have read the final version of the manuscript and approved the same. **Figure 1** is created with Biorender.com.

ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. Journal and Publisher will not be responsible for any copyright infringement and plagiarism issues.

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