

COVID-19 Vaccine Booster Shots: Do We Really Need a Third Dose? – A Review

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ABSTRACT

Background: The global reappearance of COVID-19, propelled primarily by the delta and omicron variant of SARS-CoV-2. Due to reoccurrence, the administration of COVID -19 booster shots has been considered by many countries to address impending declining immunity with the passage of time and decreased efficacy against the COVID-19 variants. The introduction of new combination of vaccines against SARS-CoV2 variants showed enhanced immunity against these variants.

Objectives: The objective of this review is to highlight the requirement of COVID-19 vaccine booster shots against evolving variants. We aimed to use the data repositories like, FDA, CDC, WHO and research articles to assess the usefulness of third dose of vaccine for preventing rise in COVID-19 cases.

Methodology: We have included English language articles in this review. The literature was investigated in PubMed and Google Scholar by use of systematic keywords. The articles are included from 2021 – 2022 and no exclusion criteria were set.

Results: The modification in the SARS-CoV-2 virulence appeared in the form of its different variants like Beta, Gamma, Delta and Omicron necessitates the administration of booster shots. Apart from the emergence of variants, the unpredictable immunity level globally as demonstrated from the ambiguous data also contributes for the need of third COVID-19 vaccine dose. To achieve immunity against evolving variants the FDA has approved the mix and match administration of different vaccines including Moderna, AstraZeneca, Pfizer-BioNTech and Janssen/Johnson & Johnson. The geriatric population and immunocompromised patients ranked as the first recipient of third booster shot because of already weakened immune system. Emphasis was also given for the accelerated and complete vaccination of population belongs to lower income countries, as the majority are yet to be vaccinated with the first dose.

Conclusion: In conclusion, research data suggests that a third dose of COVID -19 vaccine is effective in protecting the individual compared with receiving only one or two doses.

Keywords: SARS-CoV-2, Vaccine booster, COVID-19 variants

INTRODUCTION

Food and Drug Administration (FDA) and Center for Disease Control and Prevention (CDC) of United States has now authorized COVID-19 boosters and additional vaccine for some people. A booster shot against COVID given as an additional dose of a vaccine at time when defense from the original shot(s) begun to decline. This booster helps people in maintaining their immunity for a longer period. Whereas a third dose is designed to enhance the response of preliminary vaccine cycle in moderately or severely immunocompromised population. The third dose, called as an additional dose both for the dual mRNA vaccine doses and single shot vaccine recipients depending on their immune system. The FDA and the CDC advise an additional dose if you:

- Are taking cancer treatment for tumors or blood cancers
- Are taking immunosuppressant because of organ transplantation and stem cell transplantation received within the last two years
- Are taking corticosteroids in high dose that may cause immune suppression
- Are primary immunodeficient diagnosed with *Wiskott-Aldrich or DiGeorge syndrome*
- Are HIV positive with a low CD4 count or high viral load, or are not antiretrovirals to treat HIV

Whereas, World Health Organization (WHO) has stated 3 reasons why one might have an additional COVID-19 vaccine dose:

1. If you are among those who didn't respond sufficiently to the first two doses – immunocompromised people
2. Immunity that you achieved from being vaccinated starts to wane
3. The inadequate performance of vaccines against the emerging variants [1, 2].

The concept of vaccine mixing was also introduced to enhance the protection [3]. The FDA has authorized mix and match of three vaccine brands for booster, Pfizer-BioNTech, Moderna, AstraZeneca and Janssen/Johnson & Johnson. The safety of the booster dose from a different brand was established by FDA and it is Pfizer-BioNTech vaccine only authorized for booster shots in 16 and 17 years of adult population [2, 4, 5]. As of 6 June 2021 Canada,

France, Germany, Norway, Denmark and Sweden were among those countries who advocated the mixing of vaccines [6].

People who are vaccinated with two doses prevents infection and if get infected reduces the impact of infection with decreased severity, infection transmission and death. The third dose plans were revealed by UK's *Joint Committee on Vaccination and Immunization (JCVI)*. They claim that a third dose is required in case if the effectiveness of the initial two jabs reduces with time, and to deal with new Covid-19 variants that is delta and omicron. But what does the evidence say? Researchers have investigated the encouraging results regarding the stability of immunity to COVID-19. There are specialized white blood cells called lymphocytes are mainly focused. These lymphocytes are either B – cells that make antibodies, and T cells, helping the B-cell to respond or promptly kill the COVID-19 virus. Antibodies stops the replication of virus once they entered the body. The antibody levels can be measured easily in a blood sample, but there is a variation in the data obtained from COVID-19 infected or vaccinated individuals. Some individuals can show satisfactory level of antibodies that can be detected for at least 7 months. Whereas some individuals have low levels of antibodies that can fall immediately after infection or vaccination. This kind of inconsistency in the antibody levels generates ambiguous data for assessing the long term immunity to COVID-19. To get deep insight, other immunity markers should also be considered i.e. B and T cells, emphasized in a recent preprint that is to be reviewed by other researchers. The study evaluated the response of functional T-cell against COVID-19, identified approximately six months after infection. Likewise, another research waiting to be reviewed, focuses on the retention capacity of B cells that are measurable in future COVID -19 exposure where antibody levels are too low to be detected. This is not the case in geriatric population of >80 years of age because of weakened immune system, when they infected or vaccinated their immunity may wane more rapidly. So, they ranked first when it comes for booster doses. Though, the data from older population shows promising results. Additionally, latest preprint has demonstrated that vaccination produces robust immune response in aged individuals [7-9]. There is evidence of diminished immunity specifically against delta-variant. Studies have concluded that Pfizer-BioNTech and AstraZeneca's single shot provides only 30% efficacy against delta,

whereas two doses increases this percentage to 88% for Pfizer and 67% for AstraZeneca [10, 11]. Another study from researchers suggested that those who were vaccinated during early episode of pandemic with Pfizer vaccine only have a substantially higher risk of infection compared to those who are vaccinated later. This risk indicates that BNT162b2 (Pfizer) vaccines fails to sustain prolong immunity against delta variant of SARS-CoV-2. However, the impact of vaccination administration timing on disease severity, symptomatic infection or hospital admission were not considered in this study [12]. Researchers from the Oxford University stated that even though third shot boosts the immunity, there is no sign for the necessity of third dose rather global administration of first dose which must be given an urgent priority [13].

Its November 26, 2021 another SARS-CoV-2 variant first detected in Botswana and South Africa named Omicron by WHO [14, 15]. Multiple mutations at the receptor binding site of spike-protein of omicron has been observed [16]. Diminished neutralizing antibody response to the omicron variant was also confirmed through laboratory data but after administration of booster dose neutralizing activity was improved [17-19]. Mild disease caused by beta and delta variant also demonstrate reasonable reduced vaccine effectiveness [20-23]. Immunity built by initial vaccination decline with delta variant [24] however, third dose provides prompt and significant boost in defense against mild and severe disease [7, 12, 25-27].

The surge of omicron variant in England was noted after a patient expired after contracting the SARS-CoV-2 omicron variant. The infectious diseases department of University of Oxford suggested that a 3 shot vaccination schedule is essential for omicron variant. Consequently, Pfizer-BioNTech and Moderna have stated that they will produce omicron specific vaccine with 100 days with modifications in the primary vaccine. It was also observed that the virus is no more looks like Wuhan strain and so new modified vaccines are required for booster shots [28].

All these studies are extremely encouraging. Moreover, confidence is developing regarding the durability of immunity against COVID -19, although further investigation is required. Nonetheless, currently there is no convincing evidence that community's immunity requires topping up with a booster jab or not [27, 29].

Recommendations Of Covid-19 Vaccine Booster in Children and Teens

According to CDC children at 5 years of age or older must receive vaccine against COVID-19. Those who are 12 years and older must receive booster shot additionally. The only vaccine which is currently approved for administration in this population (5 – 17 years) is Pfizer-BioNTech [30].

Current Vaccines and Emerging Covid Variants

European Centre for Disease Prevention and Control (ECDC) frequently evaluates most recent evidence on COVID -19 variants identified through *rules-based genomic variant screening* and *epidemic intelligence* or other *technical resources*. ECDC reports the data in the form of tables which are updated as **add, remove or change** variant information based on the decision (Table – 1). These tables are thoroughly reviewed by ECDC and WHO Regional Office for Europe's joint virus characterization working group. The weekly country wise COVID variant surveillance report published on ECDC website:

- **“Rapid Risk Assessment:** Assessing SARS-CoV-2 circulation, variants of concern, non-pharmaceutical interventions and vaccine rollout in the EU/EEA, 15th update” – 10th June 2021.
- **“Threat Assessment Brief:** Implications for the EU/EEA on the spread of the SARS-CoV-2 Delta variant of concern” – 23rd June 2021 [31].

Currently, numerous variants of the coronavirus are being considered as variants of concern (VOCs) like *beta, gamma delta and omicron*. VOCs spread more easily with high disease severity, or they may be unresponsive towards vaccines. Early data obtained from Public Health England (awaiting review) suggest that vaccines still protect against the worst impact of disease caused by gamma, delta and beta variants ranging from reduced disease severity to robust protection. The vaccination is working, immunity is lasting and protecting us against the complications of COVID-19 this is what evidence are showing up till now. But the main point of concern regarding booster doses is that the major proportion of the world, specifically low-income countries unable to meet the targeted vaccination goal and as little as 1% of the eligible adults have received their first jab [32] [9].

Table 1. ECDC Current Evidence on COVID Variants.

WHO Label	Lineage+ additional mutation	Country first detected (Community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Transmission in EU/EEA
Beta	B.1.351	South Africa	K417N, E484K, N501Y, D614G, A701V	September 2020	Increased (v) (1)	Increased (v) (2,3)	Increased (v) (4,5)	Community
Gamma	P.1	Brazil	K417T, E484K, N501Y, D614G, H655y	December 2020	Increased (v) (6)	Increased (v) (7)	Increased (v) (5)	Community
Delta	B.1.617.2	India	L452R, T478K, D614G, P681R	December 2020	Increased (v) (8)	Increased (v) (9-11)	Increased (v) (10-12)	Community
Omicron	B.1.1529	South Africa and Botswana	(x)	November 2021	Increased (v) (13-15) a	Increased (v) (16)	Unclear (v) (17,18) b	Community

Inadequate vaccination facilitates the virus to flourish. The virus can mutate easily when it infects and reproduces in many thousands of people, a reason for the emergence of new variants. Thus, the high level of viral transmission areas no doubt can be a cause for VOC's emergence. To date seven variants of interest have emerged so far from the areas of high viral transmission and have the potential to be VOC's. They are under monitoring to assess the level of threat they could pose. There is an urgent need to go ahead of virus globally in to prevent the appearance of more VOC's. So far, the data does not give robust recommendations for the third dose of covid vaccine in rich countries, rather it is much better to give these doses to countries with low first dose coverage. Since we cannot truly escape from this pandemic until we have high vaccine coverage worldwide [32].

Performance Evidence of Booster Vaccination

Regulatory authorities has authorized booster vaccination in numerous territories, and the products are labelled as BNT162b2, mRNA 1273 and Ad26.COVS.2.S. Additionally, clinical trials data for booster doses of vaccines like ChAdOx1-S [recombinant] and CoronaVac, COVID-19 vaccine BIBP, BBV152 and NVX-CoV2373 are available. To date all studies, demonstrate robust extended immunological response (following primary immunization) either by attaining or enhancing the peak antibody levels. However, the data obtained is insufficient for the assessment of kinetics and duration of the response. Whereas booster regimens

that are homologous and heterologous are efficient immunologically. Increasing number of countries are publishing their data regarding the vaccine effectiveness for booster doses but with limited follow-up. Overall improvement in protection against infection, disease severity, hospitalization and reduction in deaths have been demonstrated by all the studies so far [33].

However, vaccine won't be our only weapon against omicron. Antiviral could also prevent infections from progressing into severe cases. Pfizer's antiviral pill Paxlovid and Merck's molnupiravir are under clinical trials [31]. COVID -19 booster shots are the same ingredients (formulation) as the current COVID-19 vaccine. While in case of Moderna COVID-19 vaccine booster shot, the dose is half of the amount of vaccine [34].

Covid Booster Side Effect

After vaccination one might experience temporary symptoms such as swollen arm where the shot is administered, fever, chills, body aches, headache, fatigue that will persist for one or two days along with or without lymph nodes swelling. The following symptoms are the signs of immune system response towards booster shot that ultimately builds up defense against SARS-COVID-19 [30].

CONCLUSION

Data from small-scale clinical trials and post-licensure studies regarding safety and reactogenicity of vaccine mixing is available but with limited investigation.

Although, combination of different vaccines is widely implemented with a vision to achieve lasting immunity against the rapidly modifying SARS-CoV-2 virus. Similarity in the safety profile as of the second dose of the primary series has been observed. Real world evidence of significant improved protection from the booster shots against SARS-CoV-2 delta and omicron variants also supports the administration of third or fourth vaccine dose. Ultimately, severity and fatality of the disease is reduced, further monitoring is required to assess the duration of defense retained with booster vaccine dose.

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