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Review

mRNA-based COVID-19 Vaccines Booster Dose: Benefits, Risks, and Coverage

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Abstract.
The number of COVID-19 vaccine-rich countries that have started COVID-19 third-dose booster programs is growing dramatically despite the lack of robust evidence on the effectiveness, safety, and frequency of the required booster doses that make the individuals/populations immune to COVID -19 infection. Beyond the ethical dilemma, the scarcity of studies on the optimal timing for offering booster doses, eligibility criteria, and if there is any association between premature or delayed administration and the degree of protection against infection. The aim of this mini- review was to collect and analyze published data on this topic in a trial to answer some questions related to the benefits versus the risks of offering frequent boosters of mRNA vaccines for increasing the population immunity against COVID-19 infection considering the current policy of providing SARS-CoV-2 vaccine booster doses in rich countries versus those in relatively poor countries with limited access to vaccination. (www.actabiomedica.it)

Key words: BNT162b2, mRNA Vaccines, mRNA-1273, COVID-19, SARS-CoV-2, Booster Dose

Introduction

As of February 6, 2022, more than 19 million new cases of coronavirus disease 2019 (COVID-19) and slightly under 68 thousand new fatalities were recorded globally. Over 392 million confirmed cases and 5.7 million fatalities were reported globally, and more than 10 billion vaccine doses have been administered (1).

Pharmaceutical corporations and scientists worldwide have been racing to develop COVID-19 vaccines. Vaccine development often necessitates years of research and testing for effectiveness and safety (2). The concept of using mRNA vaccines is based on the idea that mRNA is an intermediary messenger that must be converted into an antigen after being delivered into host cells via multiple methods. RNA molecules have been used for research and therapeutic purposes for the last 20 years (2). The main benefits of mRNA vaccines over DNA-based vaccines are: 1) the ease and speed with which they may be manufactured; 2) the higher biosafety; and 3) the safer vector as they carry a short sequence to be translated (3).

Almost five months after reporting of the first cases of COVID-19 in China, several COVID-19 vaccines, including mRNA vaccines such as the Pfizer–BioNTech (BNT162b2) and Moderna (mRNA-1273), have been developed to stimulate the immune response using messenger RNA (mRNA) (4). Both BNT162b2 and mRNA-1273 are highly efficacious

(vaccine efficacy ranges from 94.1% - 95%) in protecting individuals from COVID-19 and are widely used globally (5-7). Table 1 shows the main COVID-19 vaccines.

The duration of effectiveness of the vaccines is generally 6 -12 months and is anticipated to slowly wane over time, especially in individuals with delta (B.1.617.2) variant (88% on average for BNT162b2 and 66% for mRNA-1273) (8,9). Several studies recently reported that mRNA vaccines' protection against COVID-19 waned swiftly following the second dose peak. Still, the hospitalization and mortality are maintained at low rates for 6 to 8 months post the second dose (5, 10-12).

With the introduction of the first and second doses of mRNA vaccines, many questions remain unanswered: a) how long does the immunity last? b) do we need booster doses of COVID-19 vaccine to keep the population immune? ; c) how frequent we can do that? and d) is there any safety issues of repeated vaccination on the short or long-term?

Many 'vaccine-rich' countries such as the UK, USA, Europe, Israel and Singapore are embarking on the 3rd booster dose of COVID-19 vaccines. However, the current evidence on the effect of giving booster doses and their effectiveness during the pandemic is still vague.

Israel offered a 3rd booster dose of mRNA vaccine (BNT162b2) to individuals aged 60 years and above in July 2021. Later, the program was expanded to include all individuals ages 12 years and above, five months post the second dose, and it was linked to the country's green vaccination passport accessibility (13).

A month later, the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) in the US authorized the use of a 3rd booster dose of COVID-19 vaccine eight months after the 2nd dose for a limited "vulnerable" group of immunocompromised individuals (14,15). As of 20th of October, the FDA expanded the booster doses authorization to include everyone 40 years and above (16).

In addition, the UK announced a booster program for all high-risk groups of individuals over 50s and those severely immunocompromised (17). On the other hand, if the mRNA vaccines cannot be offered due to hypersensitivity, the Oxford-Astra Zeneca (AZD1222) vaccine was recommended to be given for those who have already received it (18).

Recently, the European Medicines Agency (EMA) authorized a 3rd dose of the mRNA-1273 or the BNT162b2 to healthy individuals (≥18), at least 6 months after their 2nd shot and at least 28 days after their 2nd shot if they are immunocompromised. In addition, they left the door open for each country to finally approve their roll-out plan (19). The number of countries which have booster programs for high-risk groups is expanding daily with variable eligibility criteria (Figure 1).

In late November 2021, a highly mutated SARS-CoV-2 variant of concern (B.1.1.529); later referred to as Omicron, emerged and sparked "concerns" worldwide due to its high contagiousness and virulence (20,

Table 1. Main anti-COVID-19 vaccine

Name	Types	Company
BNT162b2 (Comirnaty®)	mRNA	Pfizer (New York, NY, USA) - BioNTech (Mainz, Germany)
mRNA-1273 (Spikevax)	mRNA	Moderna (Cambridge, MA, USA)
AZDI222 (Vaxzevria®,Covishield)	Adenovirus vector ChAdOx1	AstraZeneca (Oxford, UK)
Ad26.CoV2.S	Adenovirus vector Ad26.CoV2.S	Janssen Biotech Cilag, Johnson & Johnson (Raritan, NJ, USA)
Gam-COVID-Vac (Sputnik V)	Adenovirus vector Ad26 and Ad5 CoV2-S	Gamaleya Institute (Moscow, Russia)
ConvideciaTM	Adenovirus vector Ad5-nCoV	CanSino Bio (Tianjin, China)
CoronaVac	Inactivated virus	Sinovac Biotech (Beijing, China)
BBIBP-CorV	Inactivated virus	Beijing Institute of Biological Products (Beijing, China)
NVX-CoV2373 (Nuvaxovid)	Recombinant nanoparticles	Novavax (Gaithersburg, MD, USA)

21). Later, it was mentioned by *Nature* that *"The Omicron variant has also further clouded forecasts of how booster campaign will affect the pandemic's trajectory"* (22).

In January 2022, a study revealed that the antibody concentrations were raised 5-folds a week after the 4th dose of Pfizer/BioNTech 's vaccine, which was suggested to significantly improve protection against infection, hospitalization, and severe symptoms. However, these findings were concluded by a small (unpublished) trial on 154 health workers who got the 4th booster dose of BNT162b2 (23). Therefore, over half a million Israelis (prioritized for high-risk groups, including over 60 , immunocompromised, and healthcare workers) have been inoculated with a 4th dose. Israel hopes that the additional booster would prevent the Omicron version from overwhelming hospitals and shutting down normal life (24). On the other hand, the opponents of the 4th dose argued that vaccinating the entire planet every 4 to 6 months is not sustainable or affordable, and more evidence is needed to determine whether, when, and how frequently vulnerable people will require more doses.

While writing this paper, Pfizer and BioNTech Inc. initiated a trial to evaluate a new novel version of BNT162b2 tailored particularly to target the COVID-19 Omicron form on 1,400 participants. Some protection appeared to be offered by the initial two-dose vaccination regimen (25). Simultaneously, Moderna Inc. has started a similar study which is especially intended to target the Omicron variant where a total of 300 participants are intended to be enrolled in two comparative groups (26). Both clinical trials are intended to investigate the safety and tolerability of the mRNA COVID-19 vaccines while targeting Omicron variant.

The threat of the non-immune poorly vaccinated population on the well-vaccinated populations: "The proof is in the pudding".

In Israel, a study was conducted on more than one million individuals aged ≥ 60 revealed that a third booster shot has restored a protective effect similar to the 2nd dose and reduced the incidence and severity of COVID-19 (19). On the other hand, a joint statement released on the 18th August 2021 by health experts from the U.S. Department of Health and Human Services (HHS) stated that "a booster shot will be needed to maximize vaccine-induced protection and prolong its durability" (20). Andrews et al. (27) revealed that regardless of whatever primary course was taken, there was a considerable evidence that the booster dose enhanced protection against COVID-19 symptomatic

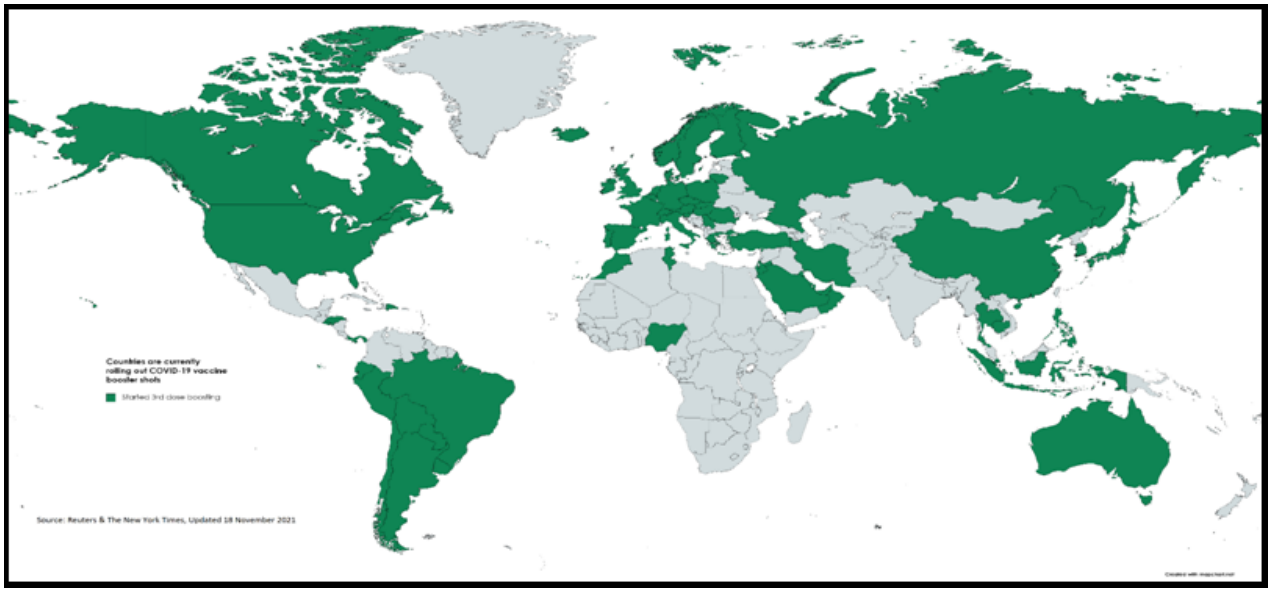

Figure 1. Countries are currently rolling out COVID-19 vaccine booster shots Europe and North America are leading the COVID-19 vaccination booster race while Africa is lagging far behind other parts of the world

patients aged over 50. In addition, numerous studies supported using booster doses with prolonged intervals to protect against emerging variants (28-31).

On the other hand, other reports have confirmed that three doses of mRNA vaccines may not be enough to protect against symptoms caused by the B.1.1.529 (Omicron) variant (32,33). It is not known if the protective immunological responses are long-lasting or not. Possibly identifying correlates of immune protection can help us understand what degree of immune biomarkers is required for protection and how this is achievable through booster optimization (34).

In summary, speeding up the vaccination efforts, including booster doses, and improving its coverage may be necessary to enhance the response to the emerging variants. This view is supported by the latest emergence of the new variant/s in Africa, with the lowest vaccination rate that produced a resurge of infection in the well-vaccinated countries.

Is it true that "No one is safe until everyone is safe"?

The World Health Organization (WHO) and a group of scientists urged vaccine-rich countries to temporarily halt or delay the third dose rollout campaigns due to several reasons. Firstly, many developing and low-income countries (e.g., Africa) struggle to vaccinate their citizens with the first and second doses. As of the 18th of October, in low-income nations, less than 4% of the population have received at least a single dosage of the vaccine, which could put the whole world at a greater risk for new variants' development (35). Secondly, the absence of robust data and evidence on the necessity for giving a 3rd booster dose for healthy individuals, as well as the vaccine's ability to protect against severe illness months after administration (36). Thirdly, the absence of studies on the ideal timing for booster doses, and whether giving a booster dose early may compromise the effectiveness of protection by the vaccine (37).

Rzymski and colleagues (38) have recently concluded that improving the immunity of wealthier populations cannot come at the price of underprivileged countries suffering from vaccine shortages. The significant immune evasion capacity of the most recent SARS-CoV-2 variant (Omicron), which originated in poorly vaccinated population, has resulted in more frequent reinfections and breakthrough infections in well-vaccinated countries who had adequate mRNA vaccine booster doses (39,40).

These data raised more discussion on the necessity of equitable access to vaccination which may be supported by using equitable access principles throughout the vaccine research and development and will end up with supply-chain processes by employing a sustainable global delivery and allocation strategies (41-43).

Does the immunity wane after infection and/or after vaccination?

Many scientists believe that there is an urgent need to explore the role of virus-neutralizing antibodies (NAbs) in predicting viral load, alleviating symptoms, and preventing hospital admissions in patients with COVID-19. The NAbs were still detected in the vast majority of patients during their second visit (96.3%), around seven months after the beginning of symptoms (44). In addition, investigators are still exploring how NAbs response to SARS-CoV-2 may give valuable insights on COVID-19 treatment and vaccination (45).

In fact, antibody responses following mRNA vaccination have been evaluated in various studies (46-48). Levin et al. (49) concluded that six months after receiving the second dose of the BNT162b2 vaccination, the humoral response was significantly reduced, particularly among men, those 65 yrs. and older, and those with immunosuppression. Another recent study by Tartof et al. (9) suggested that the substantial efficacy of BNT162b2 against hospitalizations lasted up to 6 months after being completely vaccinated, even in the face of extensive distribution of the delta variant.

Dispinseri et al. (45) found that NAbs titers gradually decline after 5–8 weeks but are still detectable in most recovered patients irrespective of co-morbidities or age of the participants. Yue et al. (50) reported that NAbs levels decreased after the second dose of inactivated vaccines. These findings suggested that a 3rd booster dosage is required to maintain the efficacy of inactivated vaccines independent of gender or two-dose vaccination protocol.

As a potential treatment option, neutralizing monoclonal antibodies (mAbs) "LY-CoV555" and "REGN-COV2" were found to hasten the natural vi-

ral load decline steadily compared to the placebo group in phase 2 trials (51,52). Garcia-Beltran et al. (53) highlighted the possibility of variants' evading neutralizing humoral immunity and the importance of developing wide safeguarding therapies against the evolving pandemic.

In summary, the decline in vaccination efficacy against SARS-CoV-2 infections is more likely due to decreasing immunity over time rather than to the delta variant evading vaccine protection. However, more work is needed to determine the longevity of NAbs and mAbs and protectivity against COVID-19.

Are we skating on thin ice? Are side-effects acceptable? What are the long-term effects?

With the starting vaccination, several studies were carried out to ascertain the safety of these vaccines, since they were produced in record time (54-56). The commonest reported adverse effects of COVID-19 vaccination consist of the injection site's local reaction followed by non- specific flu-like symptoms.

However, although the mRNA vaccines have a remarkable efficiency and effectiveness in severe cases of COVID-19 with an overall acceptable safety profile, instances of serious adverse events following COVID-19 vaccinations are continuously pouring in the current scientific literature and are source of vaccine hesitancy in many persons. Serious adverse reaction following immunization is defined as a post-vaccination event that are either life-threatening, requires hospitalization, or result in severe disability (57).

High mortality rates have been reported in patients with cerebral venous sinus thrombosis (CVST) due to vaccine-induced immune thrombotic thrombocytopenia (VITT) after vaccination with adenoviral vector SARS-CoV- 2 vaccines (ChAdOx1 nCoV-19 vaccine, Ad26.COV2 vaccine) (58-61). However, the estimated incidence of VITT seems to be 1 case per 100 000 vaccine exposures (62).

Following vaccination with mRNA COVID-19 vaccines (ie, Comirnaty and Spikevax), myocarditis and pericarditis can develop within a few days of vaccination, particularly following the second dose (63-70). Furthermore, Patone et al. (71) found that the risk of myocarditis rose after the third dosage of BNT162b2 for 1 to 28 days.

Based on recent reviewed data, the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have determined that the risk for both of these conditions is overall 'very rare' (~1 in 10 000 vaccinated people may be clinically affected), with the highest risk among younger males (72).

Tsilingiris et al. (73) proposed that with the clear necessity for a booster dosage to maintain an acceptable degree of protection against COVID-19; our understanding of the epidemiological and clinical characteristics of vaccine-induced myocarditis would continue to increase indefinitely. Other researchers believed that increasing the interval between vaccine doses could help in reducing the likelihood of developing inflammatory adverse effects (74).

We do not know about the long-term effects in the affected patients. A German study suggested that 2 months after SARS-CoV-2 positivity, 78% of survivors had persistent cardiac involvement, of which 60% presented ongoing signs of myocarditis (75). Therefore, an early identification of patients with cardiac involvement is vital, so they can benefit from cardioprotective therapy and appropriate follow-up strategies (72).

The World Health Organization listed Guillain-Barré syndrome, seizures, anaphylaxis, syncope, encephalitis, thrombocytopenia, vasculitis, and Bell's palsy as serious neurologic adverse events (57).

A wide spectrum of serious neurological complications (transverse myelitis, acute disseminated encephalomyelitis and Guillain-Barré syndrome) has been reported, in form of isolated case reports or small cases series, following COVID- 19 vaccination (76,77). However, the association of these adverse events following COVID- 19 vaccination is still controversial.
Less frequently, other reactions following the administration of mRNA COVID-19 vaccines included case reports with pneumonitis (78,79), interstitial lung disease (80, 81), and cutaneous adverse reactions such as psoriasis (82,83) . However, the level of evidence is limited to case reports.
A large spectrum of cutaneous reaction patterns following the COVID-19 vaccination were reported by Kroumpouzos et al. (84). The authors searched the PubMed, Google Scholar, and Scopus databases and the preprint server bioRxiv for articles on cutaneous complications linked to mRNA-1273 (Mod-

erna), BNT162b2 (Pfizer-BioNTech), and AZD1222 (AstraZeneca-Oxford University) vaccines published until 30 September 2021. Eighty studies describing a total of 1 415 reactions were included. Cutaneous reactions were more prevalent in females (81.6%). Delayed large local reactions were the most common complication (40.4%), followed by local injection site reactions (16.5%), zoster (9.5%), and urticarial eruptions (9.0%). Injection site and delayed large local reactions were predominantly caused by the mRNA-1273 vaccine (79.5% and 72.0%, respectively). In general, 58.3% occurred after the first dose only, 26.9% after the second dose only, and 14.8% after both doses (84). BNT162b2 vaccination was more closely linked to distant reactions (50.1%) than mRNA-1273 (30.0%). Varicella zoster and herpes simplex reactivations were reported 7 days and 13 days post vaccination, respectively (84).

Factors that may compromise the effectiveness of the COVID vaccination (Mix and match strategy, new variants, side effects and the inequitable vaccination distribution)

With the increased risk of thrombolytic incidents, the use of the ChAdOx1 nCoV-19 vaccine in young individuals, especially women in Germany, was restricted in early 2021, and those who had this vaccination as the first dosage were required to receive a different vaccine for the second dose (85). Since then, several countries have started to mix and match COVID-19 vaccines (86). In addition, the continued emergence of variants of concern (VOC) such as Omicron and the inequitable worldwide coverage of vaccines will continue to limit vaccine effectiveness (87). Therefore, the third booster dose could be homologous (the same as the vaccine given earlier) or heterologous (which refers to providing a different vaccine from what was given earlier). In some cases, heterologous immunization against COVID-19 should be taken as an alternative. These cases include vaccine shortage, adverse events linked to the priming dose, and seeking better efficacy (88,89).

Atmar et al. (90) have conducted a phase ½ open-label clinical trial including 458 subjects from ten US cities and revealed that adults who had completed a first COVID-19 vaccination regimen (mRNA-1273, Ad26.CoV2.S, and BNT162b2) at least 12 weeks previously tolerated and responded well to homologous and heterologous boosters. On the other hand, a recent study by Palanica and Jeon (91) revealed that after the first vaccination dosage, individuals who got an adenoviral vector vaccine (e.g., Oxford-AstraZeneca known as AZD1222) suffered the greatest number of common side effects, as well as more severe levels of each side effect, as compared to those who received an mRNA vaccine. Participants who got mRNA-1273 as their second vaccination suffered the greatest number and severity of adverse effects after the second dosage, regardless of whether they received mRNA-1273, BNT162b2, or Oxford-Astra Zeneca as their first dose.

Collectively, data were favoring heterologous vaccination is still lacking. Further research is crucial to validate the benefits and determine the best combinations, dosages, and intervals.

Outstanding questions

Overall, the benefits and advantages of mRNA vaccines for COVID19 prevention continued to surpass any potential risks. Nevertheless, we still do not know the accurate answers to many questions:

1. How long does the immunity-induced by the booster doses last?
2. How and when we can reach fully vaccinated status?
3. Is there any need for an annual COVID-19 booster dose? If yes, is it going to be indefinite?
4. What is the longevity of neutralizing antibodies and the duration of their effective protectivity against COVID-19?
5. What are the long-term effects of adverse events? How to best diagnose and manage affected cases? For those who already had an adverse event, such as myocarditis should we advise to complete the full vaccination schedule?

In summary, the answers to these important questions need extensive, integrated, and combined public health, clinical and basic research with the collaboration of institutions, universities, ministries, countries and national and international health care organizations.

Table 2. Summary of benefits and risks associated with mRNA COVID-19 vaccines booster dose

Benefits	Risks *
Infection rate	Cardiac related complications such as myocarditis and pericarditis
Severity of Signs and Symptoms	Lung related complications such as pneumonitis and interstitial lung disease
Overall Hospitalization	Cutaneous adverse reactions such as hypersensitivity and psoriasis, including exacerbation of the symptoms
Intensive Care Unit (ICU) Hospitalization	Hematologic related such as thrombocytopenia
Death rate	Efficacy against new variants
	Waning immunity over time

* Adverse events/reactions are mostly short-term and differ according to certain demographics such as age, ethnicity, etc.

Furthermore, it appears that prospective and observational controlled studies are necessary to analyze the risk-benefit ratios of short and long-term vaccination related side-effects in different populations. The questions of whether certain populations can be identified as more suitable candidates for one or another vaccine and who and how to monitor for rare potential complication will require additional studies. Comparative risks of different vaccines are also advised.

Finally, accelerating vaccination campaigns, including booster doses, and expanding coverage equally among different populations and countries are critical for enhancing response to new variants. However, a part of the population still hesitates to recognize the dangers associated with SARS-CoV-2. Healthcare professionals remain the most appropriate advisers regarding vaccination decisions and must be supported to provide reliable and credible information. The risks and benefits of current vaccines must be compared with the real possibility of contracting the disease and developing long-term complications (Table 2).

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Declarations

Ethics approval and consent to participate.
The article describes a review article. Therefore, no additional permission from our Ethics Committee was required.

Availability of data and material
All generated data is included in this published article.

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Authors' contributions
AJN, MII: Literature Search, Manuscript Preparation. VDS edit the manuscript and the bibliography, and reviewed the section of reported adverse events after vaccination. All authors read and approved the final manuscript

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