



Adjudicating the logistics of COVID-19 vaccine boosters from a global perspective

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ABSTRACT

The emergence of the novel SARS-CoV-2 variants has led to the advocacy of COVID-19 vaccine boosters by many countries. The reasons cited for the booster vaccination, such as waning immunity, immune escape due to viral evolution and suboptimal responses in immunocompromised individuals, need to be cautiously weighed against possible risks, including immune-mediated side effects, vaccine hesitancy, global vaccine inequity, and emergence of new variants in the naive population. The scientific, ethical, and economic adjudication indicates that the primary vaccination of unvaccinated masses should be prioritized over the premature booster implementation. Although, in the future, when the global vaccine shortage has been subdued or if the protective immunity afforded by the current COVID-19 vaccination protocols wanes substantially, the booster vaccinations may be implemented.

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The ongoing coronavirus disease 2019 (COVID-19) pandemic has expedited vaccine development at an unprecedented pace. However, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) delta variant-driven global surge in infections has put the long-term effectiveness of COVID-19 vaccines under the spotlight. Therefore, many countries advocated the inoculation of COVID-19 vaccine boosters to counter breakthrough infections. However, the considerations on the need and timing of booster doses are being scrutinized by the scientific community.¹ Here, we aim to adjudicate the rationales associated with the COVID-19 booster vaccination and delineate the logistic recommendations as per the presently available scientific evidence, based on which the policymakers may draw an informed consensus.

After the complete primary immunization with the currently available COVID-19 vaccines, the boosters may be needed for several reasons such as waning of the protective immunity, emergence of the variants of concern that escape the vaccine-induced immunity, and suboptimal immune responses in certain risk groups such as immunocompromised individuals. These factors need to be carefully evaluated and weighed against the possible risks related to the premature implementation of booster protocols such as immune-mediated side effects, undermined vaccine acceptance in public, global inequity due to constrained vaccine supply, and the emergence of new highly transmissible viral variants in the unprotected masses.

The correlates of immunological protection conferred by the natural infection or vaccination against the SARS-CoV-2 have not been clearly deciphered till date, but the adaptive immunity is known to be mediated by B cells (humoral) producing neutralizing antibodies and T cells (cell-mediated) including CD8⁺, CD4⁺, and regulatory T cells.² The immunological memory of the encounter is retained by the B and

T cells. While the currently available evidence suggests the persistence of antibodies for at least 6 months post-exposure,³ the waning of neutralizing antibody titers has also been reported.⁴ Nevertheless, this should not be equated with the decline of vaccine effectiveness over time, since the long-term protection, as observed in any other vaccination, is mediated not only by the humoral immunity but also by the cell-mediated immunity and memory responses by B and T cells. After a subject is fully immunized and protective antibodies wane, the subject may become more susceptible to infection since there is less antibody in the oral and nasal cavities to prevent virus replication. However, the anamnestic immune response is triggered by such virus replication, resulting in a rapid increase in protective antibody levels, which is likely to prevent serious disease. Furthermore, the vaccines targeting the SARS-CoV-2 antigens of the initial pandemic phases can elicit humoral immune responses against the currently circulating variants,⁵ hence ruling out the evolution of the virus to the point of immune escape from available vaccines.

The assessment of the need for booster doses should ideally be based on the vaccine effectiveness against severe disease. Although some reduction in vaccine effectiveness has been observed against certain variants of concern, such as the delta variant,⁶ the currently available COVID-19 vaccines are still highly protective against hospitalization, severe disease, and death.⁷ The follow-up of breakthrough infections also suggests less severe disease than unvaccinated individuals.⁸ Even certain studies comparing the efficacy of booster doses with two-dose protocol have deduced very short-term protective effect, which does not signify noteworthy long-term protections.⁹ Although the primary vaccination series could be complemented with additional doses for certain risk groups such as the

immunocompromised individuals, which have been reported to constitute around 40% of breakthrough infections,¹⁰ but studies on the homologous and heterologous combinations for ascertaining the maximal immune responsiveness should be conducted and considered for deciding the further course.

The present side-effect profile after complete COVID-19 vaccination suggests only meager or infrequent adverse reactions; hence, it may not necessarily contribute to an increased rate post-booster. While the booster itself does convey an immunological benefit still, the early and frequent boosters without adequate data-based implementation may result in adverse immune-mediated side effects such as myocarditis, thrombosis, and Guillain-Barre syndrome, which, in turn, could also undermine public confidence causing widespread vaccine hesitancy.

Apart from tracking the evidence for the need for booster doses, the global availability of vaccines is also an essential factor to consider. Large-scale boosters may augment the vaccine inequity, which is already rampant due to constraints in the global vaccine supply. Around 3.5 billion people constituting nearly half of the worldwide population have not yet received even the first dose of the COVID-19 vaccine.¹¹ If the booster vaccination in high-income countries (HICs) is prioritized over vaccine coverage of unvaccinated masses in lower-middle-income countries (LMICs), the resulting large-scale morbidity, mortality, and collapse of healthcare would be undeniable, and the global mitigation of the pandemic would never be achieved. The unmitigated SARS-CoV-2 transmission in such settings of unvaccinated populations might also lead to the emergence of highly transmissible or virulent variants that could escape the vaccine-induced immunity, forcing the redesigning of vaccines from scratch. However, this situation is still preventable as, despite this foreseen risk, there has not yet been a documented variant that completely escapes vaccine-induced immunity.

The economic perspective should also encourage the HICs to divert the surplus vaccine supplies to the LICs through the COVAX initiative, instead of the urgent implementation of the booster vaccination programs for their residents already protected by two doses of COVID-19 vaccines. The RAND Corporation has estimated a return of US\$4.8 for the HICs for every \$1 spent on the vaccine supply to LMICs, and the Global Dashboard for Vaccine Equity also reveals maximum gain of uniform vaccine distribution to the HICs.¹²

Conclusively, the scientific, ethical, and economic adjudication points out that the currently available COVID-19 vaccines are efficiently capable of saving lives and the benefits of administration of booster doses fall short of weighing out the primary immunization of unvaccinated masses. Therefore, the efforts of the worldwide scientific community and policymakers should be directed to continuous monitoring of the SARS-CoV-2 variants and vaccine efficacy, apart from the conduction of concrete evidence-based as well as risk group targeted studies. The current focus should be on protecting naive individuals as soon as possible, instead of wasting time and resources on large-scale boosters, which are forthwith less likely to be beneficial to the world health than primary vaccination in an under-vaccinated region. Although in the future, when the global shortage of COVID-19 vaccines is overcome or if the immunological protection afforded by

the currently available vaccination protocols wanes substantially, the booster vaccinations may be implemented. The current situation does not stipulate the strategic implementation of widespread booster vaccination campaigns from a global public health perspective.

Authors' contributions

PR. did the ideation, conceptualization, data curation, writing original draft, reviewing, and editing. O.P.C. executed the conceptualization, writing original draft, reviewing, and editing. I.S. did the reviewing and editing. All the authors critically reviewed and approved the final version of the manuscript.

Ethical approval

This article does not require any human/animal subjects to acquire such approval.

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