Letter to the Editor

Fourth dose of COVID-19 vaccine: Does it still contribute any additional immunoprotection?

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Abstract

A second booster dose of COVID-19 vaccine is a widely discussed issue globally. This letter to the editor describes on possible additional immunoprotection due to the fourth dose of COVID-19 vaccine. According to the modeling study, it can demonstrate that the fourth dosage of COVID-19 vaccination can still provide extra immunoprotection in case that previous doses are not the highly effective COVID-19 vaccines.

Keywords: Booster dose; COVID-19; Fourth; Vaccine

Dear Editor, COVID-19 is still a global emergency, with no effective disease control.[1] Vaccination is the best hope for disaster management.[2] COVID-19 immunization is now widely acknowledged as a possible useful primary COVID-19 preventive strategy. Primarily, two vaccine doses are necessary for full vaccination. However, following complete vaccination, antibody levels may fall, necessitating the use of self-protective behavior. The efficacy of the COVID-19 vaccine in specific groups of vaccine recipients with

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underlying disease is a current clinical challenge. Many types of individuals, including imumocompromised patients and those with autoimmune diseases (such as systemic lupus erythrematosus and ulcerative colitis), have a poor immune response to normal immunization.[1] The imumocompromised patients are the main primary group that is highly unresponsible to vaccinations.[1] It has been suggested that an extra-dose vaccination be given. The third dosage of COVID-19 immunization as a booster dose is already in use, and the resulting immunoprotection is an issue reported in some investigations.[2] For the fourth dose, a second booster such as that given in Israel, of COVID-19 immunization, it is now a current topic for clinical study. Only a few studies have been published, and the bulk of them is limited to people with underlying medical conditions (such as organ transplantations[3–5]). Clinical data are needed to assess if the fourth vaccine dose would be beneficial and whether overvaccination would be a risk.[1]

If a fourth dose of COVID-19 vaccine as a second booster for non-immunocompromised vaccine recipient is planned, a research should be available to confirm the vaccine's immunogenicity. The authors utilize a preliminary mathematical model analysis to assess the expected utility of the fourth dose in response to the research question "does the fourth dose of COVID-19 vaccine still contribute any extra immunoprotection?" In this scientific letter, the "fourth dose" is defined as a second booster for non — immunocompromised groups (after two-dose initial regime and a booster dose at 5—6 months later). The protection is defined as a specific infection prevention.

The current research is focused on clinical mathematical modeling. The standard technique for using mathematical modeling approach for assessment of efficacy of boostering dose of a vaccine is used.[6] The technique is a new technique for in silico assessment of vaccine efficacy and it required no subject for researching on the new vaccine that is still not

completely proven for safety.[6] In vitro and in vivo research have shown that the new technique by in silico mathematical modeling technique cab provide a good prediction result with no impact from environmental confounding factors.[6] The conceptual framework for explaining the model with simplified basic mathematical equations is presented in Figure 1.

Various vaccines have different immunogenicity mechanisms, according to a basic assumption. Diverse biotechnologies-based vaccinations have different basic components, resulting in different immunoprotection inductions. Before dropping, there will be the most effective immunity level or protective efficacy when routine vaccination is completed. The fourth and final dose will serve as a booster. The protective efficacy, or boostering effect, caused by each vaccine's second dosage is computed using basic data on the protective efficacy, or boostering effect, caused by the fourth dose. For modeling purposes, the boostering activity is defined as the vaccine's ability to increase the protective efficacy after the second dose when compared to the first dose.

For modeling purposes, it is expected that the protective efficacy will be used as background protective efficacy after the third dose. In theory, the extra protection provided by the fourth dose can raise boostering action and improve the protective efficacy rate if administered as the second dose, but it will not exceed the baseline protective efficacy rate. If a switching type of vaccination is administered as a booster for its type related first dose, the additional protection from the fourth dosage will be equal to the reported protective efficacy of the switched brand vaccine. The final protected efficacy will not, however, surpass the background protective efficacy of that new provided vaccine, which is a critical criterion for current models. Under the previously described primary condition, the final predicted protective efficacy rate after the fourth dose will be calculated as "background protective effect after the third dose + extra protection from the fourth dose." The primary data on background protective effect after the third dose in our study is based on a recent public report on immunoprotection from different third dose COVID-19 vaccinations in our setting, tropical Asia (from the Department of Disease Control's Emergency Operations Center; available at https://www.prachachat.net/marketing/news-837033). The data are national level data based on local public health registry database system (https://co-lab.moph.go.th/) and covers all adult non-immunocompromised populations of both sexes under the third dose COVID-19 vaccination governmental policies.

The results are reported in Table 1 based on clinical modeling, different third dose regimens result in different protection rates and it can result in different predicted protection efficacy for different background third dose regimens. In general, the different COVID-19 vaccines that are available and the various dosage regimen are the factors
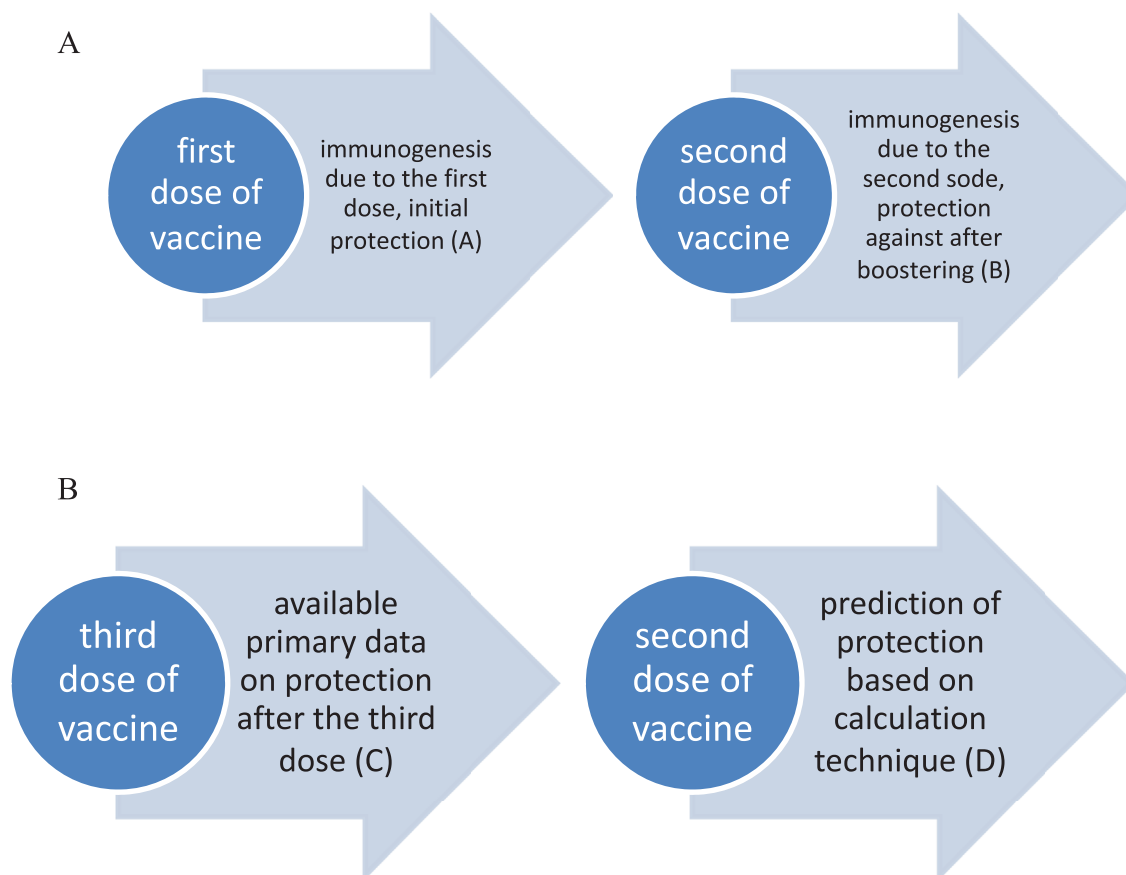

Figure 1: Conceptual framework of the model. A. Standard classical COVID-19 vaccination − calculation for basic boostering activity of the vaccine. *B − A = boostering activity of the boostering vaccine. B. Boostering with the fourth dose. *C + (B−A) = D given that C + (B−A) ≤ B.

Table 1: Expected immunoprotection after the fourth dose of COVID-19 vaccine.

The background complete third dose vaccination***	The fourth dose vaccine		Protective efficacy rate (%)	
	Type	Specific boostering* activity (%)	Background protective efficacy rate after the fourth dose** (%)	Expected protective efficacy rate after the fourth dose (%)****
A	Inactivated	27	86	86
	Viral vector	37	86	89
	mRNA	24	86	94
B	Inactivated	27	82	86
	Viral vector	37	82	89
	mRNA	24	82	94

*Specific boostering activity means ability to increase protective against infection efficacy rate to the first dose of vaccine if that vaccine is given as the second dose.

** Background protective effect after the third dose means the reported immunoprotection rate after complete three dose vaccination of that vaccine and data are based on public available data in a developing country (https://www.prachachat.net/marketing/news-837033). The primary study is a national based registry study collecting the data from third dose vaccination for the whole population in the country covering adult vaccine recipients from both sexes during July–November 2021. The data of protection is based on the follow-up surveillance of the vaccine recipients for each third dose regimen. The protection rate against infection is determined based on recorded data on COVID-19 after vaccination, regardless type or variant of SARS-CoV2.

*** mix-and-match COVID-19 vaccine administration according to local vaccination program (https://www.prachachat.net/marketing/news-837033: A = inactivated-inactivated-mRNA viral vector, B = inactivated-inactivated-mRNA.

****, the final predicted protective efficacy rate after the fourth dose will be calculated as "background protective effect after the third dose + extra protection from the fourth dose."

that might affect the vaccine efficacy.[7] The present study can reconfirm the effect of different vaccines and vaccination regimens.

It can demonstrate that the fourth dosage of COVID-19 vaccination can still provide extra immunoprotection. However, the observed impact could be explained by the fact that the background third dose COVID-19 immunization in this situation is not based on the standard mRNA COVID-19 vaccination regimen, leaving an immunological gap in which the additional fourth dose could fill (see footnote in Table 1). Due to the nature of pure clinical mathematical model study, there is no variance and no role of statistical analysis for comparison. A simple basic mathematical comparison of the results in Table 1 can be performed.

Also, the present study is based on the situation in our setting. Only 1 type of mRNA vaccine is available at the study period, therefore, there is effects of different mRNA vaccine types. In a setting with different types of mRNA COVID-19 vaccine, further evaluation to compare the effect of different type of vaccine is required. As earlier mentioned, the background third dose regimen in the study setting is not based on mRNA vaccines, therefore, the protective efficacy after the third dose of vaccine was still not the highest level and it means there is a gap that the additional fourth dose vaccine can add.

In the current situation of the emerging variants, such as omicron variant, the usefulness of the fourth dose should be carefully discussed. It is reported that the omicron variant might be associated with decreased vaccine induced protection. This means there is a decreased background protective effect after the third dose. Based on the present model, the significant increasing level of protection after applying the fourth dose might be expected. The fourth dose vaccine might be an interesting alternative for management of merging omicron variant. It should be further studied comparable to other new proposed alternative such as

multivalent vaccine. In case of multivalent vaccine, it still required a period of waiting time for a success in development and the extra dose of the new vaccine is similarly required.

Finally, some other options to further vaccinations should be discussed. For some specific groups of patients, such as those with immune deficiencies, alternative ways to promoted immunity should be further studied. Examples of interesting way for promoting protection against infection include using pre-exposure prophylaxis with antibodies (such as Evusheld[8]).

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Conflict of interest

The authors declare no conflict of interest.

Ethical approval

This is a mathematical model based study and required no ethical approval.

Consent

Not applicable.

Authors contributions

RM 50 5 ideas, drafting, writing, analyzing, final approval for submission.

VW 50% ideas, supervising, final approval for submission. All authors have critically reviewed and approved the

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