

## Expected Response to the Additional Fifth Dose of COVID-19 Vaccine

Dear Editor,

COVID-19 is still a global emergency with no effective treatment.<sup>[1]</sup> Vaccination is the best option for managing the spread of this disease.<sup>[2]</sup> COVID-19 vaccination is now universally acknowledged as an effective primary COVID-19 preventive strategy. Traditionally, two vaccine doses are necessary for full vaccination. After complete vaccination, immunity levels may diminish, necessitating the use of self-protective behavior. When there is a new developing variant and a potential decline in antibodies after completion of routine immunization, several experts recommend using an additional booster dose of the COVID-19 vaccine.<sup>[3,4]</sup> In general, vaccine effectiveness against COVID-19 infection wanes significantly 5-8 months after completion of immunization, which is why COVID-19 vaccine booster injections are required. Booster dosages should be administered only if there is strong evidence that they will reduce hospitalization, severe disease, and mortality.<sup>[5]</sup> A single booster dosage is advised for adults aged 16 and up, 3 months after the initial course, according to the Australian Technical Advisory Group on Immunisation (ATAGI) (<https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/advice-for-providers/clinical-guidance/clinical-recommendations>). For patients at risk of severe COVID-19, a second booster dose is suggested 4 months after the first.

In many settings, such as Israel and Southeast Asian countries, the third dose of the COVID-19 vaccine is commonly used.<sup>[5,6]</sup> In those areas, Israel and Southeast Asian countries, the fourth boosting is already in use.<sup>[7]</sup> In the case of the introduction of a new strain, as well as the likely loss of public immunity following routine mass vaccination, some scientists are recommending a fifth dose vaccine for the most at-risk immunocompromised groups, such as transplant recipients and dialysis patients.<sup>[8]</sup> In some settings, such as Cambodia, the local public health plan aims to immunization the local medical personnel with the fifth dose of the COVID-19 vaccine (<https://www.bangkokbiznews.com/world/1005783>). Because the efficacy of the fifth vaccine dose is unknown, any investigation into its efficacy is intriguing. To evaluate response to the fifth dose of the COVID-19 vaccine, the authors of this study used a clinical model technique.

The current research is focused on clinical mathematical modeling. According to an *in vitro* and *in vivo* investigation, the technique is typical *in silico* mathematical modeling technique with no impact from environmental confounding factors. "Primary data"<sup>[9]</sup> refers to basic information on the protective efficacy rates of various vaccination types. A basic

assumption is that distinct vaccinations have different immunogenicity mechanisms. Vaccines based on various biotechnologies include a variety of basic components, resulting in a variety of immunoprotection inductions. The highest effective immunity level or protective efficacy will be obtained once routine immunization is completed. The extra fifth dose will be utilized to help the immune system function more effectively.

The modeling strategy utilized in this investigation is the same as that employed in a previous study to examine the effect of a COVID-19 vaccination booster dosage. Following the fourth dose, the protective efficacy is likely to be treated as background protective efficacy for modeling purposes.<sup>[10]</sup> If given as a boosting dosage, the extra protection from the fifth dose can increase boosting activity and raise the protective efficacy rate, but it will not exceed the baseline protective efficacy rate. However, the end protection efficacy will not surpass the background protective efficacy of the boosting vaccine, which is a requirement for current models. As a result, the efficacy of the third dose will be the same as the background protective efficacy of the ordinary second dose. Under the previously described primary condition, the final projected protective efficacy rate after the fifth dose will be calculated as "background protective effect after the fourth dose + extra protection from the fifth dose."

The basic data from a developing Asian location with a problem of highly endemic uncontrollable infection are utilized in this model to simulate and anticipate the role of COVID-19's fifth dose. Background COVID-19 immunization varies in this scenario, with some patients receiving heterologous two doses of COVID-19 plus two booster doses of COVID-19 vaccine. For the current modeling study, the most recent publicly available public data on the efficacy of the fourth dose of the COVID-19 vaccine were used. The primary data is available online from a real-life government report in Southeast Asia (<https://www.tnnthailand.com/news/covid19/108553/>).

According to the report, the efficacy of the fourth dose of COVID-19 for protecting against infection is 84.7%. According to the modeling study, the expected efficacy of the fifth dose of vaccine against infection is presented in Table 1. Based on the modeling, the expected protective efficacy rates after the fifth dose of COVID-19 vaccine for the fifth dose vaccination using inactivated, viral vector, and mRNA type COVID-19 vaccine are 86.9%, 89.9%, and 94%, respectively, from the baseline protective level of 84.7%.

The fifth dose of vaccine still has a role in increasing immunity and all kinds of vaccines have a role but the best vaccine for boosting is the mRNA vaccine. It has been

**Table 1: Expected immunoprotection after the fifth dose of COVID-19 vaccine**

Type	The fourth dose vaccine	Protective efficacy rate (%)	
	Specific boosting* activity (%)	Background protective effect before the new additional dose** (%)	Expected Protective efficacy rate after the fifth dose (%)
Inactivated	27	84.7	86
Viral vector	37	84.7	89
mRNA	24	84.7	94

\*Specific boosting activity means ability to increase protective efficacy rate to the first dose of vaccine if that vaccine is given as the second dose. \*\*Background protective effect before the new additional dose means the reported immunoprotection rate after complete four dose vaccination of that vaccine and data are based on public available data in a developing country(<https://www.tnmtailand.com/news/covid19/108553/>).

noted that protection begins to fade after receiving the COVID-19 vaccination, posing a danger of re-infection. After obtaining both doses of vaccine, COVID-19 infection is still possible, so prevention is essential. Furthermore, immunity in some specific groups, such as dialysis patients, is not good after two doses of vaccine.<sup>[11]</sup> As a result, the boosting immunization dose has been suggested and is already being used in many settings. Only a few studies have been done on the efficacy of the additional boosting vaccine dose, and they are mostly limited to select populations with immunological deficiencies.<sup>[8,12-14]</sup> Many scientists now feel that a boosting vaccine dose can increase immune response, but that it isn't always required.<sup>[5]</sup>

The third dose of the COVID-19 vaccine is widely used to promote immunity in immunocompromised hosts and to combat emerging COVID-19 variants.<sup>[5]</sup> Due to unsuccess in disease control, some settings such as those in Indo-China already used an additional fourth dose of vaccine. After the fourth dose, the vaccine efficacy is still questionable. Many studies have shown that the boosting fourth dose can still play a role in immunogenetic against the currently circulating COVID-19 variant.<sup>[15,16]</sup> Nevertheless, the problem of disease control still exists. Scientists in some specific areas with background use of low effective first and second doses of COVID-19 vaccine raise a question of whether the fifth dose of COVID-19 vaccine is required or not.

The current model models and predicts the role of the fifth dose of COVID-19 using primary data from a developing Asian region with a problem of highly endemic uncontrollable infection. In this investigation, the fifth dose boosting COVID-19 vaccine regimen was found to have a role in immunogenicity against the infection. Background COVID-19 immunization varies in this scenario, with some using heterologous conventional two doses of COVID-19 plus two boosting doses of COVID-19 vaccine. The fifth dose of the COVID-19 vaccine is effective for improving immunity.

In conclusion, the fifth dose-boosting COVID-19 vaccine regimen was discovered to play a role in infection immunogenicity in this study. If a fifth dose COVID-19 vaccine is planned, different types of COVID-19 can

provide an increased immune level. Compared to the mRNA type of vaccine, the other types of vaccines are not far from the mRNA type vaccine in terms of efficacy. Further studies to specifically assess the exact additional immunogenic as well as clinical utility outcome (prevention of COVID-19 infection and death) of the different types of boosting COVID-19 vaccine should be performed.

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### Conflicts of interest

There are no conflicts of interest.

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