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COVID-19 vaccine booster strategy: striving for best practice

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As we enter the third year of the COVID-19 pandemic, policy makers need pragmatic data about the performance of the different vaccination regimens for informed decisions and prioritisation, because placebo-controlled studies are no longer feasible for ethical reasons. Furthermore, there is a need for evidence of the protective effectiveness of the vaccines against symptomatic or severe COVID-19 in real-world settings, in which unselected individuals from every age and different risk groups are vaccinated.

In *The Lancet Global Health*, Alejandro Jara and colleagues[1] report the effectiveness of CoronaVac (Sinovac Biotech), AZD1222 (Oxford-AstraZeneca), and BNT162b2 (Pfizer-BioNTech) boosters after the completion of a primary schedule with two doses of CoronaVac. The results are based on the analyses of real-world data from a dataset gathered from a single centralised immunisation registry of nearly 11·2 million individuals aged 16 years or older, representing 80% of the Chilean population. Participants in the study cohort were followed up until Nov 10, 2021; therefore, the study follow-up potentially excludes the three omicron subvariants (BA.1, BA.1.1, and BA.2).

Compared with no vaccination, the adjusted vaccine effectiveness against symptomatic COVID-19 was calculated as 78·8% (95% CI 76·8–80·6) with three doses of CoronaVac, 96·5% (96·2–96·7) for a BNT162b2 booster, and 93·2% (92·9–93·6) for a AZD1222 booster. The adjusted vaccine effectiveness rates were 86·3% against hospitalisation and 86·7% against COVID-19-associated deaths following a three-dose CoronaVac schedule. Corresponding rates were higher for the two heterologous schedules, at 96·1% for a BNT162b2 booster and 97·7% for a AZD1222 booster against hospitalisation and 96·8% for a BNT162b2 booster and 98·1% for a AZD1222 booster COVID-19-associated deaths. Additional analyses indicated that a three-dose CoronaVac schedule provided improved vaccine effectiveness and a high level of protection against severe outcomes and death than a two-dose CoronaVac schedule. Although a heterologous booster strategy showed higher vaccine effectiveness, it is of note that the median age of women and men who received CoronaVac was 69·1 years, compared with 43·5 years for women and 45·2 years for men who received a BNT162b2 booster and 67·0 years for women and 66·3 years for men who received an AZD1222 booster. The difference in median age is of note when evaluating the relatively lower effectiveness of a three-dose CoronaVac regimen because it has been shown that both the antibody and the T-cell responses are compromised in people aged 55 years or older.[2]

Although the study by Jara and colleagues[1] supports a so-called mix-and-match approach, the optimum strategies and dosing intervals to provide maximum benefit in the context of the SARS-CoV-2 variants in circulation need to be defined. Zeng and colleagues[3] reported that neutralising antibody titres induced by two doses of CoronaVac declined to near or below the lower limit of seropositivity after 6 months; however, a third dose given 8 months after the second dose led to a strong boost in immune response. Aikawa and colleagues[4] showed that a third dose of CoronaVac 6 months after the completion of an initial two-dose CoronaVac series resulted in a robust immunogenicity response even in patients with autoimmune rheumatic diseases, with a greater benefit in those who were still seronegative for COVID-19 after the first two vaccinations. Khong and colleagues[5] reported that different combinations of CoronaVac and BNT162b2 (BNT162b2-CoronaVac-BNT162b2 or CoronaVac-CoronaVac-BNT162b2) vaccines in a three-dose regimen induced high neutralising antibody titres even for the delta (B.1.617.2) variant, but a much lower titre for the omicron BA.1 subvariant. Two-dose vaccination regimens even with mRNA vaccines showed a rapid and pronounced loss of protection against symptomatic infection with the omicron variant[6] and for severe disease even before the surge of the omicron variant.[7] Because the results reported by Jara and colleagues[1] do not cover the omicron surge, we cannot estimate the effectiveness of the three-dose schedules in those settings. McMenamin and colleagues[8] analysed the data from Dec 31, 2021, to March 8, 2022, to estimate the vaccine effectiveness of BNT162b2 and CoronaVac vaccines covering the fifth wave of COVID-19 with omicron BA.2 lineage in Hong Kong. Three doses of both vaccines were shown to be highly protective against severe disease and mortality in all age groups, yet the effects of heterologous vaccination have not been investigated.

The results of the study by Jara and colleagues[1] provide insights to policy makers on how to manage the booster dose strategy after two doses of CoronaVac vaccination. It is now clear that, in a world where vaccine equity is a utopia, scientists can only strive for how to best use the available vaccines to reach for a maximum attainable benefit. A mix and match vaccination strategy, including inactivated vaccines for priming and heterologous boosters thereafter, seems to be a realistic policy.

We declare no competing interests.

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