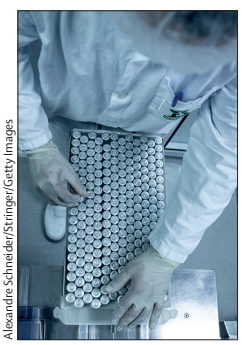
Boosting immunity after CoronaVac



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Recent evidence has shown that COVID-19 immunity and vaccine effectiveness wanes over time.[1] Together with the emergence of the omicron (B.1.1.529) variant with substantial antibody escape,[2] this resulted in widespread implementation of booster vaccinations to optimise immunity and protection. With increasing availability of vaccines and evidence towards improved immunogenicity of heterologous vaccine regimens,[3] knowledge on the immunogenicity of different vaccine combinations and how to best induce booster immunity is of paramount importance to guide vaccination policies. A homologous third dose of CoronaVac (Sinovac) given 8 months after the second dose was shown to be associated with an increase in detectable antibodies,[4] whereas immunogenicity data for heterologous boosting was unknown.

In *The Lancet*, Sue Costa Clemens and colleagues provide timely results of a randomised trial on the reactogenicity and immunogenicity of a homologous and three different heterologous booster vaccines among individuals who had received two doses of the CoronaVac vaccine.[5] A total of 1240 individuals from São Paulo and Salvador, Brazil, without history of SARS-CoV-2 infection were randomly assigned to receive a third dose with either CoronaVac, the mRNA vaccine BNT162b2 (Pfizer–BioNTech), or one of the vector vaccines ChAdOx nCov-19 (AstraZeneca), or AD25.COV2-S (Janssen). Adult study participants were recruited to include two equally sized age groups: younger than 60 years and 61 years and older. 1205 individuals, of whom 729 (60·5%) were women and 814 (67·6%) were White, were available for analysis of primary outcomes, which included reactogenicity and immunogenicity of IgG antibodies and neutralising activity before the boost and 28 days after.[5]

Three serious adverse events possibly related to the vaccine occurred, which resolved completely. Otherwise, all booster doses were well tolerated with commonly observed local and systemic reactions predominantly found after heterologous boosting. Local pain at the injection site was most frequent among recipients of BNT162b2, whereas systemic adverse events predominated among vector recipients. This safety profile is reassuring and will likely not influence the choice of booster vaccine in clinical practice. Antibody concentrations were remarkably low 6 months after the primary vaccine doses (20·4% [95% CI 12·8–30·1] in adults younger than 60 years and 8·9% [4·2–16·2] in older individuals), and were induced in all study groups by day 28 after boosting. Another recent study from Hong Kong confirmed low median antibody titres in individuals vaccinated with CoronaVac 4 months after primary vaccination.[6] Although CoronaVac recipients in the present study had the most favourable safety profile, the magnitude of the antibody boost was significantly lower compared with all heterologous regimens. As exemplified for IgG titres, the increase from baseline to 28 days was 12-fold for CoronaVac, 152-fold for BNT162b2, 90-fold for ChAdOx, and 77-fold for AD25.COV2-S. This effect held true for all immunological parameters including neutralising activity, where the booster effect was most pronounced in recipients of BNT162b2, followed by the two vector vaccines where immunogenicity was largely similar. Neutralising capacity towards the delta and omicron variants were well induced after heterologous boosting in more than 90% of individuals. By contrast, only 80% and 35% of individuals after CoronaVac boosting had neutralising activity towards delta and omicron, respectively. Across all vaccines, responses after boosting were lower in the older age group than in the younger group.[5]

Although the COV-BOOST study with different vaccine combinations has shown a similar advantage of mRNA and vector vaccines over adjuvanted protein-based vaccines,[7] the rapidly spreading omicron variant underscores the need for large cohort studies to determine whether the differences in immunogenicity after booster vaccination observed with age and vaccine regimens will correlate with different susceptibility towards infection or disease. Additionally, with increasing immune escape, there is a need for diagnostic assays adapted to characterise vaccine-induced humoral and cellular immunity towards specific SARS-CoV-2 variants, which should also include determination of meaningful correlates for

protection.[8,9] Of note, the present study did not assess T-cell immunity, which could inform on the ability to protect from severe disease and which was shown to be markedly induced after heterologous vector or mRNA vaccination in healthy and immunocompromised individuals.[3,10]

Among approximately 10 billion vaccine doses administered globally, CoronaVac accounts for more than 2 billion doses, making it the world's most frequently used SARS-CoV-2 vaccine.[11] It is noteworthy to mention that there are considerable price differences between the SARS-CoV-2 vaccines, which could influence the choice of booster vaccines in low-income and middle-income countries. However, as a result of WHO's endorsement of heterologous vaccine schedules[12] and Costa Clemens' study, we strongly believe that heterologous boosting with mRNA or vector vaccines after primary CoronaVac vaccination should be advised to rapidly regain protective antibody concentrations.

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