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Booster doses for inactivated COVID-19 vaccines: if, when, and for whom

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Dealing with vaccine equity and at the same time ensuring adequate protection for the most vulnerable is essential to reduce the burden of COVID-19. New questions have been challenging the scientific community and policy makers after the initial rollout of mass vaccination campaigns, particularly surrounding the potential waning of vaccine effectiveness. It is still unknown whether supplemental doses are needed, and researchers are working to determine if, when, and for whom booster doses would be helpful for the prevention of COVID-19 illness and pandemic control.

As of the time of writing, the inactivated whole-virus vaccine CoronaVac is the most widely offered COVID-19 vaccine in the world.[1] In *The Lancet Infectious Diseases*, Gang Zeng and colleagues report a randomised controlled trial embedded in a phase 2 trial to evaluate a third dose of CoronaVac after the two-dose schedule in healthy adults.[2] When a third dose was administered 8 months after the second dose, there was a three-fold to five-fold increase in neutralising antibody (NAb) titres against the original virus of SARS-CoV-2 compared with the NAb after the second dose. Notably, the authors also reported that a homologous third dose had a favourable safety profile. The high concentrations of NAb in adults of all ages after a third dose show that CoronaVac was able to generate immune memory, bringing hope that more people around the world who received, or will receive, inactivated vaccines against COVID-19 will be protected.

Variants of concern (VOCs) have been a source of increased case rates of breakthrough COVID-19 infections among the vaccinated population. A main limitation of Zeng and colleagues' study[2] is that the concentrations of NAbs against different VOCs were not evaluated. Yue and colleagues[3] evaluated 53 volunteers who received the two-dose schedule of CoronaVac and a booster dose 8 months later. The level of NAb against the original variant was similar to that reported by Zeng and colleagues, but there was a 4·2-fold reduction in neutralising antibody titres against the delta (B.1.617.2) variant compared with the original variant.[3] The same reduction of neutralising antibodies against the delta variant was found in a subgroup of volunteers 28 days after the second dose.[3] Vacharathit and colleagues[4] evaluated CoronaVac's immunogenicity after the second dose, finding that NAb titres against the delta variant were lower than NAb titres against the original virus and other variants. Therefore, it is expected that the results of Zeng and colleagues' study would be different if the authors had tested NAb titres against the delta variant or other VOCs after the booster dose. Although NAb titre is not an exclusive determinant of clinical protection, it is correlated with vaccine efficacy against symptomatic disease.[5]

The reduction in NAb titres after 6 months of the first two-dose scheme of CoronaVac was remarkable. NAb titres against the original variant declined to near or below the seropositive cutoff of 8 UI/mL,[2] as previously shown for the gamma (P.1) variant.[6] On this topic, Zeng and colleagues add evidence on how to optimise the timing of the booster dose. The NAb titres in participants receiving a third dose after 8 months were higher than those in participants receiving a third dose 2 months after the second dose.[2] Further studies should systematically evaluate and model when to administer a booster dose, but based on existing evidence, it seems a larger interval than 2 months is needed. A point to consider when making decisions about the intervals between doses is whether booster doses are going to be used in a mass immunisation campaign to prevent outbreaks of VOCs, when long-term effectiveness might not be the primary objective.

Currently, no data are available on effectiveness of a booster dose for inactivated whole-virus COVID-19 vaccines. Only one study using an mRNA vaccine shows preliminary results: a 95·6% efficacy of mRNA vaccine booster after 5 months.[7] Because of the pronounced decrease of NAbs titres[2,6,8] and reduced effectiveness in the older population,[9] WHO's Strategic Advisory Group of Experts on Immunization recommend a third dose of inactivated virus vaccines or a heterologous booster for people aged 60 years and older who already have received the two-dose scheme.[10]

Effectiveness and cost-effectiveness studies to evaluate the protection from, and waning immunity of, third doses of inactivated virus vaccines are needed

to generate robust recommendations, especially in the context of VOCs. Key research questions include whether homologous or heterologous booster vaccines should be used, which scheme should be administered for those with an inadequate response to the primary vaccination schedule, and whether to use new vaccines specifically designed to work against VOCs. Importantly, on the basis of current knowledge, it is expected that protection against severe outcomes is maintained for the healthy, non-vulnerable population, who therefore will not necessarily need a booster dose.

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