Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

A protein subunit vaccine booster following two doses of inactivated SARS-CoV-2 vaccine provides high neutralisation of SARS-CoV-2 and its variants in mice

SARS-CoV-2 vaccination provides good protection against severe illness and death from COVID-19; however, the waning of immunity against SARS-CoV-2 in fully vaccinated individuals has been reported mostly 6 months after the last vaccine dose.[1-3] A booster vaccination (third dose of vaccine) has been proposed and initiated in many countries; and a prime-boost sequential immunisation approach is thought to be beneficial.[4]

We designed a prime-boost experiment of the inactivated vaccine BBIBP-CorV (Sinopharm) and receptor-binding domain (RBD)-based tandem-repeat dimeric protein subunit vaccine ZF2001 (Zhifei Longcom) in mice (appendix p 6).

First, we assessed five groups: BBIBP-CorV-ZF2001 (one dose BBIBP-CorV followed by one dose ZF2001), ZF2001-BBIBP-CorV group (one dose ZF2001 followed by one dose BBIBP-CorV), ZF2001-ZF2001 (one dose ZF2001 followed by second dose ZF2001), BBIBP-CorV-BBIBP-CorV (one dose BBIBP-CorV followed by second dose BBIBP-CorV), and a placebo group. The highest geometric mean titre (GMT) of neutralising antibodies was 14 469 in the BBIBP-CorV-ZF2001 group, which was 14·5 times that of the GMT of neutralising antibodies in the ZF2001-BBIBP-CorV group, and more than four times that of the GMT of neutralising antibodies in the ZF2001-ZF2001 and BBIBP-CorV-BBIBP-CorV groups. Moreover, the BBIBP-CorV-ZF2001 group elicited the highest GMT of neutralising antibodies against all SARS-CoV-2 variants in this study (appendix pp 4–9).

At the time of writing, more than half of the Chinese population have received two doses of inactivated SARS-CoV-2 vaccine.

Second, we investigated the booster efficacy of ZF2001, assessing four groups: BBIBP-BBIBP-ZF2001 group (two doses of BBIBP-CorV, followed by one dose [booster] ZF2001), BBIBP-BBIBP-BBIBP group (two doses of BBIBP-CorV, followed by third dose [booster] BBIBP-CorV), BBIBP-BBIBP group (two doses of BBIP-CorV and no booster), and a placebo group. The BBIBP-BBIBP-ZF2001 group (appendix pp 6 and 10) showed the highest level of RBD-specific IgG, spike protein-specific IgG, and neutralising antibodies; the GMT of neutralising antibodies was 21 375, which was 3·4 times more than in the BBIBP-BBIBP-BBIBP group. The BBIBP-BBIBP-ZF2001 group also kept a consistent neutralisation against the SARS-CoV-2 variants, including kappa (B.1.617.1) and lambda (C.37), and the GMT of neutralising antibodies were higher than in any other groups (appendix p 6; –1·2 to 1·2 fold change compared with prototype, p>0·05). In addition, using ZF2001 as a booster in the BBIBP-BBIBP-ZF2001 group provided a high level of GMT of neutralising antibodies (18 667) against SARS-CoV-2 delta variant (B.1.617.2); four times (4633) that of the GMTs in the BBIBP-BBIBP-BBIBP group and 14·6 times (1279) that of the GMTs in the BBIBP-BBIBP group. The BBIP-BBIP-ZF2001 group still had a GMT of neutralising antibodies of 18 635 against the most immune-escape variant of concern, beta (B.1.351), which is 8·6 times that of the BBIBP-BBIBP-BBIBP group (2157). Using ZF2001 as a booster vaccine elicits higher antibody response against SARS-CoV-2 wild type and SARS-CoV-2 variants in this study (appendix pp 4–10).

Compared with the BBIBP-CorV (inactivated vaccine), ZF2001 elicits a more focused antibody production by using SARS-CoV-2 spike RBD dimer as the antigen. Using two doses of BBIBP-CorV vaccine to prime and ZF2001 as a booster vaccine, the B cells producing RBD-specific antibodies—which takes up most of the neutralising antibodies—will be further activated.[5] Based on evidence that ZF2001 as a booster vaccine following two inactivated vaccines could increase the neutralising antibody titre, especially for variants including delta, a heterologous booster vaccine using ZF2001 could be considered for the future immunisation programme.

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See **Online** for appendix

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