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**Supplementary Data**

**Delta (B.1.617.2) inactivated vaccine candidate elicited neutralizing antibodies to SARS-CoV-2 and circulating variants in rhesus macaques**

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**Material and methods**

***Virus titration and vaccine preparation***

Zhejiang Provincial Center for Disease Control and Prevention carried out the screening of Delta variant strains from throat swab samples of imported cases in Zhoushan in 2021. Viral titers of SARS-CoV-2 were measured using a microdose cytopathic effect (CPE) assay. Virus samples were diluted 10-fold in series, mixed with Vero cells at a density of 3–5 × 104 in a 96-well plate, and checked for the presence of cells under a microscope after 4 days in a 5% CO2 incubator at 37 °C. Virus titers were determined using the Karber method (Ramakrishnan, 2016). Viruses were produced in a 10-layer cell factory at 37 °C. The virus solution was collected at 48–96 h after inoculation, inactivated with 1:4000 β-propiolactone at 2–8 °C for 20–24 h, and then purified using chromatography. The purified virus was mixed with Al(OH)3 adjuvant to prepare a candidate vaccine for SARS-CoV-2.

***Validation of virus inactivation***

We inoculated inactivated Delta SARS-CoV-2 vaccine into monolayer Vero cell T75 culture flasks, cultured at 37°C, and passaged every 4 days for 3 consecutive passages. The cytopathic conditions of each passage were observed. This experiment was repeated three times. At the same time, a negative control (normal Vero cells) experiment was performed. There was no CPE observed in each generation, and the negative control cells were also free of lesions.

***qRT-PCR***

Total RNA was extracted from organs with a QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany) and a HiScript® II One Step qPCR SYBR® Green Kit (Vazyme Biotech Co., Ltd, Nanjing, China). The forward and reverse primers targeting the *S* gene were used: RBD-qF1: 5′-CAATGGTTAAGGCAGG-3′; RBD-qR1: 5′-CTCAAGGTCTGGATCACG-3′. RT-PCR was performed under the following reaction conditions: 50 °C for 3 min, 95 °C for 30 s, and then subjected to 40 cycles of 95 °C for 10 s and 60 °C for 30 s.

***Analysis of vaccine immunogenicity in rodent***

144 female BALB/c mice (6–8 weeks old) and female SD rats (6–8 weeks old) were provided by Beijing Weitong Lihua Experimental Animal Technology Co., Ltd. 144 BALB/c mice were randomly divided to receive two immunization schedules, D0/D14 or D0/D28. Each immunization program was divided into six groups: low (5 μg/dose with adjuvant, n = 12), medium (10 μg/dose with adjuvant, n = 12), high (20 μg/dose with adjuvant, n = 12), negative control (normal saline, n = 12), adjuvant control (10 μg/dose, n = 12), and medium dose (10 μg/dose) without adjuvant. Each BALB/c mouse received five separate injections (~ 0.1 mL per injection) for a total injection volume of 0.5 mL per mouse. The D0/D14 immunization schedule of SD rats was the same as that of the BALB/c mice, while the D0/D28 immunization schedule was divided into five groups: low, medium, high, adjuvant control, and medium dose without adjuvant. Each SD rat received two separate injections (~ 0.25 mL per injection) for a total injection volume of 0.5 ml per SD rat. All animals were injected intramuscularly, the conditions of the animals were observed, and blood was collected at the indicated times to detect serum specific anti-S1 protein IgG antibodies and the neutralizing activity against Delta (B.1.617.2) in the serum to analyze the immunogenicity of the vaccine.

***Virus stocks***

Vaccine strain SARS-CoV-2/Vero/LXG/2021/ZJ28 (Delta/B.1.617.2/EPI\_ISL\_1911196) was isolated from throat swab samples cultured in Vero cells. The prototype strain (No. CWV20200701B) was isolated by Rong An bio-pharmaceutical Co., Ltd. and five SARS-CoV-2 mutant strains were isolated from the throat swab and cultured in Vero cells in the Biosafety Level 3 Virology Laboratory (Zhejiang Center for Disease Control and Prevention, Hangzhou, China), including SARS-CoV-2/Vero/HMJ/2021/ZJ15 (Alpha), SARS-CoV-2/Vero/LXG/2021/ZJ28 (Delta/B.1.617.2/EPI\_ISL\_1911196), SARS-CoV-2/E6/DSh-P3/2022/ZJ25(Omicron/B.1.1/EPI\_ISL\_12040149), SARS-CoV-2/E6/ChXQ/2022/ZJ46 (Omicron/BA.2.3), and SARS-CoV-2/E6/FJH/2022/ZJ104 (Omicron/BA.5.2). The challenge experiment uses a strain sourced from the National Pathogen Microorganism Strain Preservation Center, with the specific code of CSTR.16698.06.NPRC 6.CCPM-B-V-049-2105-8. This strain also belongs to the B.1.617.2 lineage of the Delta variant, but it is different from the strain used for vaccine development. They were harvested at 80% cytopathogenic efficiency (CPE) and viral titers were determined by microdose CPE assay. All virus stocks were sequenced with Illumina NextSeq to verify that they contained the expected spike protein sequence and no changes to the furin cleavage sites.

***Serum neutralizing assay***

Serum was inactivated in a water bath for 0.5 h at 56 °C, and then serially diluted to the required range. The diluted serum was mixed with 200 CCID50/100 μL (the virus dose that can infect 50% of the cell culture) of the virus suspension in a ratio of 1:1. And a normal cell control without infection was set. The cells were incubated in a CO2 incubator (37 ± 1 °C) for 96 h. Then, 200 CCID50/100 μL of virus solution was diluted to 10−1–10−3 and mixed with cells. Each dilution was repeated in eight wells, and a normal cell control was set at the same time, followed by culture for 96 h. Neutralization endpoints were calculated by observing the CPE under an inverted microscope. We then calculated the mean titer for each group by summing the individual titers and dividing by the number of samples in that group. Next, we calculated the logarithm (base 10) of each mean titer, and then calculated the overall mean of these logarithmic values. Finally, we took the antilogarithm of the overall mean to obtain the GMT.

***Serum antibody titers were determined by enzyme-linked immunosorbent assay (ELISA)***

Add recombinant SARS-CoV-2 Spike S1 protein (His Tag) diluted to 2 µg/mL with CBS coating buffer (cat: CB07100, Thermo, Germany) to a 96-well plate, overnight at 2–8°C, and block with 3% BSA for 1 h at room temperature. Add diluted serum to each well and incubate at 25 °C for 1 h, washed with PBS three times, then add HRP-conjugated goat anti-mouse antibody (cat: SSA007, Sino Biological, China) and incubate at 25 °C for 1h. Use TMB to develop, then add 2mol/L H2SO4 to stop the reaction, and measure the OD value at 450 nm by ELISA plate reader [SpectraMax M5 (YO525), Molecular Device, USA].

***Safety evaluation***

SD rats (6–7 weeks) were obtained from Beijing Vital River Laboratory Animal Technology Co., Ltd. Twenty SD rats (10/gender) were used in the single-dose toxicity test and were randomly divided into 2 groups (5/gender/group), which were the negative control group and the experimental group, respectively. Animals in the negative control group were given a single intramuscular injection of 0.9% sodium chloride; animals in the experimental group were given 4 doses/animal (10 μg/dose) of the inactivated vaccine (Vero cells, Delta strain) by a single intramuscular injection. All animals were administered at the gastrocnemius and quadriceps muscles of both hindlimbs, and the administration volume was 2 mL per SD rat. The injection volume for each point of all the above-mentioned animals was 0.25 mL. During the experiment, the SD rat’s death/moribundity, clinical symptoms, body weight and food intake were observed and recorded. All animals were euthanized on D15, gross anatomy was observed, abnormal tissues were fixed, and histopathological examination was performed.

Cynomolgus monkeys (3.5–5.5 years old) were purchased from Guangxi Frontier Biotechnology Co., Ltd. Repeated dosing toxicity test used 30 cynomolgus monkeys, randomly divided into 3 groups, including negative control group and two experimental groups (low dose, high dose, n = 5/gender/group). The administration route of animals in each group was single-point or multi-point intramuscular injection into the quadriceps femoris muscle of the right hind limb, and the injection volume at each point did not exceed 0.5 mL. The animals in the negative control group were given 0.9% sodium chloride injection (2.5 mL/only); the low-dose group was administered 1 dose/animal in an injection volume of 0.5 mL (containing 10 μg of sample), and the high-dose group was administered 5 doses/animal in an injection volume of 2.5 mL (containing 50 μg of sample). One injection was administered at D1, D15, D29 and D43, respectively, for a total of 4 injections. During the experiment, the clinical observation, body weight, body temperature, electrocardiogram, blood pressure, eye examination, clinical pathology (blood count, coagulation function, blood biochemistry, urinalysis), T lymphocyte subsets (CD3+, CD3+CD4+, CD3+CD8+, CD3+CD4+/CD3+CD8+), serum cytokines (IL-2, IL-4, IL-5, IL-6, TNF-α, IFN-γ), C-reactive protein, serum complement (C3, C4), and serum-specific IgG antibodies against the SARS-CoV-2 S1 protein were monitored. Three days after the last dose (D46) and the end of the 4-week recovery period (D71), the animals were euthanized, and dissected. The main organs were weighed, the ratios of viscera to body and brain to brain were calculated, and pathological examination of various tissues and organs were performed.

Guinea pigs (4–5 weeks) were obtained from Beijing Vital River Laboratory Animal Technology Co., Ltd. The whole-body active allergic reaction test was performed using 36 female guinea pigs, randomly divided into 4 groups: negative control group, positive control group, and experimental group (low and high dose groups), with 9 animals in each group. The negative control group was given sodium chloride injection; the positive control group was given human serum albumin (HSA) at a sensitization dose of 20 mg/each and an excitation dose of 40 mg/each. HAS (2020114140) was purchased from Chengdu Rongsheng Pharmaceuticals Co., Ltd. The low and high dose groups were given the inactivated vaccine (Vero cells, Delta strain) In the low-dose group, the sensitization dose was 0.1 dose, and the stimulation was 0.2 dose, and in the high-dose group, the sensitization dose was 1 dose, and the stimulation was 2 dose. The concentration/content of each dose was 10 μg/0.5 mL. Sensitization was administered by intramuscular injection once in D1, D3, and D5, and a total of 3 injections were administered. The first three animals in each group were stimulated 14 days after the last sensitization (D19) and the last six animals in each group were stimulated 21 days after the last sensitization (D26). The animals in each group were observed for signs of allergic reactions after stimulation. All surviving animals were euthanized at the end of the excitation observation.

***Challenge assay in rhesus macaques***

Twelve rhesus monkeys (5–6 years old) were purchased from Hubei Tianqin Biotechnology Co., Ltd. (6/gender) and were divided into three groups (2/gender/group): four in the adjuvant group; four in the low-dose vaccine group, given 10 μg of inactivated vaccine intramuscularly; and four in the high-dose vaccine group, given 20 μg of inactivated vaccine intramuscularly. The administration volume was 0.5 mL/animal. All macaques were immunized on days 0 and 28. Peripheral blood was collected on day 36 and 42 for neutralizing antibody testing. After anesthesia, at 21 days after the second immunization (D49), SARS-CoV-2 was administered by the intratracheal route with a viral load of 1 × 105 TCID50. During the attack experiment, the general signs of each animal were recorded daily, as well as their body weight and body temperature. Peripheral blood and throat swabs were collected daily and routine blood biochemical tests as well as viral load measurements were performed. On day 7 post-infection, the animals in each group were euthanized and six lung lobes were collected for pathological, virological, and immunological analyses.

***Phylogenic tree analysis***

The genome sequences of Delta variant vaccine strains were obtained by second-generation sequencing, and phylogenetic trees were mapped using mafft(Katoh et al., 2002) and fasgtree (Price et al., 2010) software to analyze the homology of the vaccine strains with other prevalent strains of the new coronavirus. The sequences used to map the evolutionary tree included whole genome sequences of approximately 500 endemic strains from the GISAID database (https://www.gisaid.org/). The inferred maximum likelihood tree was plotted by ggtree(Yu et al., 2017).

***Western blotting***

Samples containing 25 uL of protein (harvested, concentrated virus solution, purified virus solution) were mixed with the loading buffer and then boiled at 100 °C for 5 min. The proteins were separated by 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene difluoride (PVDF) membranes (300 mA, 55 min). Blots were blocked with 5% skimmed milk containing phosphate-buffered saline with 0.1% Tween-20 (PBST) at 37 °C for 2 h, and then subsequently mixed with anti-N protein rabbit Ab (1:1000, cat: 40143-R004, Sino Biological, China) and anti-S protein rabbit Ab (1:1000, cat: 40589-T62, Sino Biological, China) placed at room temperature and incubated on a horizontal shaker with slow shaking for more than 30 min, followed by incubation at 4 °C overnight. The membranes were incubated with secondary antibody goat anti-rabbit IgG H&L (HRP) (GE NA934, 1:5000, Abcam, UK) at room temperature on a horizontal shaker with slow shaking for 1 h. Protein bands were visualized using enhanced chemiluminescence (Azure Biomolecular Imager, USA).

***Electron microscopy (EM) sample preparation***

For cryo-EM sample preparation, a 3 μL aliquot of purified viral particles was applied to a glow-discharged C-flat R2/1 Cu grid. Grids were manually blotted for 3 s in 100% relative humidity for plunge-freezing (Vitrobot; FEI) in liquid ethane, as described previously (Wang et al., 2019). All samples were examined on a microscope (Titan Krios, FEI Company, Eindhoven).

***Pathological Analysis***

The lung tissues were fixed in 4% paraformaldehyde for paraffin embedding. These tissue specimens were sectioned into 4-μm-thick slices. The standard H&E staining protocol was followed for tissue staining, and the changes in lung tissues were observed under a light microscope (DM2500, Leica, Wetzlar, Germany).

***Statistical analysis***

Data are presented as the mean ± standard deviation. Statistical analyses were conducted using GraphPad Prism 9.4.1 (GraphPad Inc., La Jolla, CA, USA). Statistics by one-way ANOVA with Tukey’s multiple comparisons test or Kruskal-Wallis test with Dunn’s multiple-testing correction. *P* < 0.05 was considered significant.

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**Supplementary Fig. S1** Vaccine strain biological information. **A** SARS-CoV-2 maximum likelihood phylogenetic tree. The SARS-CoV-2 isolates used in this study are indicated with black arrows and labeled. **B** Schematic diagram of the 3D structure (Delta PDB: 7w9i) and mutation site of the full-length S protein of the vaccine variant.

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**Supplementary Fig. S2** Vaccine virus stability and inactivation verification. **A** Determination of virus titer after the serial passage of the vaccine seed lot. **B** The effect of inoculation MOI on the inactivated vaccine stock virus titer. **C** Inactivation kinetics of three batches of virus supernatant.

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**Supplementary Fig. S3** Evaluation of vaccine immunogenicity and cross-immune protection. Inactivated vaccine (Vero cells, Delta strain) was administered to BALB/c mice and SD rats using different doses (0.9% NaCl, adjuvant, low, medium and high dose with adjuvant, and medium dose without adjuvant) and different immunization schedules (injection at D0/D14 and D0/D28), respectively. Serum collection times were all calculated from the first immunization (D0). Serum specific IgG antibody levels against Delta (B.1.617.2) in BALB/c mice (**A, B**) and SD rats (**C, D**). Serum neutralizing antibody levels in BALB/c mice (**E, F**) and SD rats (**G, H**). **I–L** Cross-neutralizing antibody activity against SARS-CoV-2 prototype and its variants. Animal serum samples were collected at D56. Cross-NAb titer against 200 CCID50/100 μL of viruses was determined in BALB/c mouse (**I, J**, n = 5) and SD rat (**K, L**, n = 10). Statistical analysis was performed by One-way ANOVA with Tukey’s multiple comparisons test (**A–D**) or Kruskal-Wallis test with Dunn’s multiple-testing correction (**E–L**) was applied.

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**Supplementary Fig. S4** The blood routine data of rhesus macaques after viral challenge. Kruskal-Wallis test with Dunn’s multiple-testing correction was applied.

**References**

Edara VV, Pinsky BA, Suthar MS, Lai L, Davis-Gardner ME, Floyd K, Flowers MW, Wrammert J, Hussaini L, Ciric CR, Bechnak S, Stephens K, Graham BS, Bayat Mokhtari E, Mudvari P, Boritz E, Creanga A, Pegu A, Derrien-Colemyn A, Henry AR, Gagne M, Douek DC, Sahoo MK, Sibai M, Solis D, Webby RJ, Jeevan T, Fabrizio TP. 2021. Infection and vaccine-induced neutralizing-antibody responses to the sars-cov-2 b.1.617 variants. N Engl J Med, 385: 664-666.

Katoh K, Misawa K, Kuma K, Miyata T. 2002. Mafft: A novel method for rapid multiple sequence alignment based on fast fourier transform. Nucleic Acids Res, 30: 3059-3066.

Lee I-J, Sun C-P, Wu P-Y, Lan Y-H, Wang I-H, Liu W-C, Tseng S-C, Tsung S-I, Chou Y-C, Kumari M, Chang Y-W, Chen H-F, Lin Y-S, Chen T-Y, Chiu C-W, Hsieh C-H, Chuang C-Y, Lin C-C, Cheng C-M, Lin H-T, Chen W-Y, Chiang P-C, Lee C-C, Liao JC, Wu H-C, Tao M-H. 2022. Omicron-specific mrna vaccine induced potent neutralizing antibody against omicron but not other sars-cov-2 variants. bioRxiv: 2022.2001.2031.478406.

Li B, Deng A, Li K, Hu Y, Li Z, Shi Y, Xiong Q, Liu Z, Guo Q, Zou L, Zhang H, Zhang M, Ouyang F, Su J, Su W, Xu J, Lin H, Sun J, Peng J, Jiang H, Zhou P, Hu T, Luo M, Zhang Y, Zheng H, Xiao J, Liu T, Tan M, Che R, Zeng H, Zheng Z, Huang Y, Yu J, Yi L, Wu J, Chen J, Zhong H, Deng X, Kang M, Pybus OG, Hall M, Lythgoe KA, Li Y, Yuan J, He J, Lu J. 2022. Viral infection and transmission in a large, well-traced outbreak caused by the sars-cov-2 delta variant. Nat Commun, 13: 460.

Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, Simmons R, Cottrell S, Roberts R, O'Doherty M, Brown K, Cameron C, Stockton D, McMenamin J, Ramsay M. 2021a. Effectiveness of the pfizer-biontech and oxford-astrazeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in england: Test negative case-control study. Bmj, 373: n1088.

Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, Stowe J, Tessier E, Groves N, Dabrera G, Myers R, Campbell CNJ, Amirthalingam G, Edmunds M, Zambon M, Brown KE, Hopkins S, Chand M, Ramsay M. 2021b. Effectiveness of covid-19 vaccines against the b.1.617.2 (delta) variant. N Engl J Med, 385: 585-594.

Price MN, Dehal PS, Arkin AP. 2010. Fasttree 2--approximately maximum-likelihood trees for large alignments. PLoS One, 5: e9490.

Ramakrishnan MA. 2016. Determination of 50% endpoint titer using a simple formula. World J Virol, 5: 85-86.

Suryawanshi RK, Chen IP, Ma T, Syed AM, Brazer N, Saldhi P, Simoneau CR, Ciling A, Khalid MM, Sreekumar B, Chen PY, Kumar GR, Montano M, Garcia-Knight MA, Sotomayor-Gonzalez A, Servellita V, Gliwa A, Nguyen J, Silva I, Milbes B, Kojima N, Hess V, Shacreaw M, Lopez L, Brobeck M, Turner F, Soveg FW, George AF, Fang X, Maishan M, Matthay M, Greene WC, Andino R, Spraggon L, Roan NR, Chiu CY, Doudna J, Ott M. 2022. Limited cross-variant immunity after infection with the sars-cov-2 omicron variant without vaccination. medRxiv.

Wang H, Zhang Y, Huang B, Deng W, Quan Y, Wang W, Xu W, Zhao Y, Li N, Zhang J, Liang H, Bao L, Xu Y, Ding L, Zhou W, Gao H, Liu J, Niu P, Zhao L, Zhen W, Fu H, Yu S, Zhang Z, Xu G, Li C, Lou Z, Xu M, Qin C, Wu G, Gao GF, Tan W, Yang X. 2020. Development of an inactivated vaccine candidate, bbibp-corv, with potent protection against sars-cov-2. Cell, 182: 713-721.e719.

Wang N, Zhao D, Wang J, Zhang Y, Wang M, Gao Y, Li F, Wang J, Bu Z, Rao Z, Wang X. 2019. Architecture of african swine fever virus and implications for viral assembly. Science, 366: 640-644.

Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, Tan W, Wu G, Xu M, Lou Z, Huang W, Xu W, Huang B, Wang H, Wang W, Zhang W, Li N, Xie Z, Ding L, You W, Zhao Y, Yang X, Liu Y, Wang Q, Huang L, Yang Y, Xu G, Luo B, Wang W, Liu P, Guo W, Yang X. 2021. Safety and immunogenicity of an inactivated sars-cov-2 vaccine, bbibp-corv: A randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis, 21: 39-51.

Xia S, Duan K, Zhang Y, Zhao D, Zhang H, Xie Z, Li X, Peng C, Zhang Y, Zhang W, Yang Y, Chen W, Gao X, You W, Wang X, Wang Z, Shi Z, Wang Y, Yang X, Zhang L, Huang L, Wang Q, Lu J, Yang Y, Guo J, Zhou W, Wan X, Wu C, Wang W, Huang S, Du J, Meng Z, Pan A, Yuan Z, Shen S, Guo W, Yang X. 2020. Effect of an inactivated vaccine against sars-cov-2 on safety and immunogenicity outcomes: Interim analysis of 2 randomized clinical trials. Jama, 324: 951-960.

Xiang T, Wang J, Zheng X. 2022. The humoral and cellular immune evasion of sars-cov-2 omicron and sub-lineages. Virol Sin, 37: 786-795.

Yu G, Smith DK, Zhu H, Guan Y, Lam TT-Y. 2017. Ggtree: An r package for visualization and annotation of phylogenetic trees with their covariates and other associated data. Methods in Ecology and Evolution, 8: 28-36.

Zang J, Zhang C, Yin Y, Xu S, Qiao W, Lavillette D, Wang H, Huang Z. 2022. An mrna vaccine candidate for the sars-cov-2 omicron variant. bioRxiv: 2022.2002.2007.479348.

Zhang NN, Zhang RR, Zhang YF, Ji K, Xiong XC, Qin QS, Gao P, Lu XS, Zhou HY, Song HF, Ying B, Qin CF. 2022. Rapid development of an updated mrna vaccine against the sars-cov-2 omicron variant. Cell Res, 32: 401-403.

Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, Han W, Chen Z, Tang R, Yin W, Chen X, Hu Y, Liu X, Jiang C, Li J, Yang M, Song Y, Wang X, Gao Q, Zhu F. 2021. Safety, tolerability, and immunogenicity of an inactivated sars-cov-2 vaccine in healthy adults aged 18-59 years: A randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis, 21: 181-192.

Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W. 2020. A novel coronavirus from patients with pneumonia in china, 2019. N Engl J Med, 382: 727-733.