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Infectious Diseases

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Han B, Song Y, Li C, et al. Safety, tolerability and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. *Lancet Infect Dis* 2021; published online June 28. https://doi.org/10.1016/S1473-3099(21)00319-4.

Appendix 1 Immunogenic Detection Method

Detection Method of Neutralization Potency against Live SARS-CoV-2

Micro cytopathic effect assay was adopted.

Serum treatment: all serum samples were inactivated at 56℃ in a water bath for 30 minutes.

Medium addition: the cell maintenance medium was added to the cell control group at 100μl/well, and 50 μl/well of maintenance medium was supplemented to the to-be-tested serum group, virus back titration group and positive control group from the second dilution.

Dilution of the serum sample: The serum was diluted four-fold (60 μl sample + 180 μl maintenance medium) with cell maintenance medium (2% newborn calf serum-199 (2% sodium hydrogen carbonate) cell maintenance medium). The diluted serum was added to the cell plate at 100 μl/well, and each sample was diluted to 2 wells in parallel. 50 μl of the mixture in the first dilution was pipetted into the next dilution, and the mixture was pipetted up and down for 8-10 times. The mixture was diluted to the appropriate dilution range by this method, and 50 μl of the last dilution was discarded, and 50 μl of the diluted sample was retained in each well.

Dilution of the virus for neutralization: the SAR-CoV-2 used for neutralization was diluted to $100CCID_{50}$/0.05ml by titer.

Neutralization: Serum of different dilutions was mixed with $100CCID_{50}$/0.05ml virus liquid in equal volume (50μl+50μl), respectively, and then incubated in an incubator at 36.5℃, 5%CO_2 for 2h.

Experimental control: Negative serum control, positive serum control, serum sample and cell control were set simultaneously.

Virus Back Titration: The virus suspension diluted to 100 $CCID_{50}$/0.05 mL was diluted via ten-fold serial dilution, i.e. diluted to 10 CCID50/0.05 ml, 1 $CCID_{50}$/0.05 mL and 0.1 CCID50/0.05 ml, and added to the 96-well cell plate respectively, 12 well per dilution and 50 μl per well, then 50 μl of cell maintenance medium was added to each well, and the plate was incubated in an incubator at 36.5°C, 5% CO2 for 5 days.

Cell Inoculation and Culture: After incubation, 100μL of Vero cell suspension (cell concentration: 1.0-2.0×105 cell/ml) was added to each well, and then incubated in an incubator at 36.5°C, 5% CO2 for 5 days.

Interpretation of the Results: It was observed for the cytopathic effect after cultured for 3-5 days, and the neutralizing antibody titer of the to-be-tested serum sample was determined according to the observation results of the cytopathic effect (CPE) on the 5^{th} day. The reciprocal of the highest serum dilution without cytopathic effects the end titer. When 1 of the 2 wells of the highest dilution serum shows CPE, while the other does not, the reciprocal of the dilution should be the neutralizing antibody titer of the serum specimen; the reciprocal of the mean dilution of the two wells should be the neutralizing antibody titer of the serum specimen when the 2 wells with the highest dilution are completely pathological while the adjacent 2 wells with low dilution are not pathological completely; when 1 of two adjacent wells is pathological while the other not, the reciprocal of the average dilutions of 2 wells should be the neutralizing antibody titer of the serum specimen. For example, 2 wells with high dilution of 1:16 have a complete CPE, while the adjacent 2 wells with low dilution of 1:8 have no CPE; or in 2 adjacent wells with dilutions of 1:8 and 1:16, one has a CPE, while the other does not. In this case, the reciprocal 12 of the average dilutions of 2 wells is the neutralizing antibody titer of the serum

Appendix 2 Safety results

Table 2-1: Adverse reactions reported within 28 days after the first and the second dose of vaccine or alum only in phase 1 and phase 2

	1.5μg group (n=219)		3μg group (n=217)		Alum only group (n=114)		Total (n=550)		P value
	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)	
Solicited adverse reactions within 0-7 days									
Any	103	51(23%)	92	59(27%)	29	22(19%)	224	132(24%)	0·276
Grade 1	75	39(18%)	71	51(24%)	20	15(13%)	166	105(19%)	0·065
Grade 2	26	16(7%)	21	19(9%)	9	9(8%)	56	44(8%)	0·824
Grade 3	2	2(1%)	0	0(0%)	0	0(0%)	2	2(<1%)	0·356
Injection site adverse reactions									
Pain	44	36(16%)	41	35(16%)	2	2(2%)	87	73(13%)	<0·0001
Grade 1	41	34(16%)	41	35(16%)	2	2(2%)	84	71(13%)	<0·0001
Grade 2	3	2(1%)	0	0(0%)	0	0(0%)	3	2(<1%)	0·356
Swelling	3	3(1%)	7	6(3%)	1	1(1%)	11	10(2%)	0·496
Grade 1	0	0(0%)	4	4(2%)	0	0(0%)	4	4(1%)	0·053
Grade 2	3	3(1%)	3	3(1%)	1	1(1%)	7	7(1%)	1·000
Induration	0	0(0%)	2	2(1%)	0	0(0%)	2	2(<1%)	0·198
Grade 1	0	0(0%)	2	2(1%)	0	0(0%)	2	2(<1%)	0·198
Erythema	0	0(0%)	1	1(<1%)	0	0(0%)	1	1(<1%)	0·602
Grade 1	0	0(0%)	1	1(<1%)	0	0(0%)	1	1(<1%)	0·602
Pruritus	4	3(1%)	2	2(1%)	0	0(0%)	6	5(1%)	0·640
Grade 1	4	3(1%)	2	2(1%)	0	0(0%)	6	5(1%)	0·640
Systematic adverse reactions									
Fever	9	9(4%)	13	11(5%)	5	5(4%)	27	25(5%)	0·931
Grade 1	3	3(1%)	2	2(1%)	2	2(2%)	7	7(1%)	0·886
Grade 2	4	4(2%)	11	10(5%)	3	3(3%)	18	17(3%)	0·225
Grade 3	2	2(1%)	0	0(0%)	0	0(0%)	2	2(<1%)	0·356
Cough	8	5(2%)	8	8(4%)	5	5(4%)	21	18(3%)	0·474
Grade 1	4	1(<1%)	4	4(2%)	3	3(3%)	11	8(1%)	0·188
Grade 2	4	4(2%)	4	4(2%)	2	2(2%)	10	10(2%)	1·000
Headache	9	6(3%)	5	4(2%)	3	3(3%)	17	13(2%)	0·818
Grade 1	5	3(1%)	4	3(1%)	1	1(1%)	10	7(1%)	1·000
Grade 2	4	4(2%)	1	1(<1%)	2	2(2%)	7	7(1%)	0·385
Anorexia	5	3(1%)	4	4(2%)	2	2(2%)	11	9(2%)	0·915
Grade 1	2	1(<1%)	3	3(1%)	2	2(2%)	7	6(1%)	0·516
Grade 2	3	3(1%)	1	1(<1%)	0	0(0%)	4	4(1%)	0·540
Diarrhoea	2	2(1%)	2	2(1%)	5	4(4%)	9	8(1%)	0·164
Grade 1	2	2(1%)	2	2(1%)	5	4(4%)	9	8(1%)	0·164
Nausea	5	3(1%)	3	2(1%)	2	2(2%)	10	7(1%)	0·886
Grade 1	5	3(1%)	3	2(1%)	2	2(2%)	10	7(1%)	0·886
Mucocutaneous eruption	2	2(1%)	2	2(1%)	1	1(1%)	5	5(1%)	1·000
Grade 1	1	1(<1%)	1	1(<1%)	0	0(0%)	2	2(<1%)	1·000
Grade 2	1	1(<1%)	1	1(<1%)	1	1(1%)	3	3(1%)	1·000
Vomiting	3	3(1%)	1	1(<1%)	1	1(1%)	5	5(1%)	0·845

	1.5μg group (n=219)		3μg group (n=217)		Alum only group (n=114)		Total (n=550)		P value
	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)	
Grade 1	3	3(1%)	1	1(0%)	1	1(1%)	5	5(1%)	0·845
Muscle pain	5	4(2%)	0	0(0%)	0	0(0%)	5	4(1%)	0·078
Grade 1	2	2(1%)	0	0(0%)	0	0(0%)	2	2(<1%)	0·356
Grade 2	3	2(1%)	0	0(0%)	0	0(0%)	3	2(<1%)	0·356
Fatigue	4	1(<1%)	1	1(<1%)	1	1(1%)	6	3(1%)	1·000
Grade 1	3	1(<1%)	1	1(<1%)	1	1(1%)	5	3(1%)	1·000
Grade 2	1	1(<1%)	0	0(0%)	0	0(0%)	1	1(<1%)	1·000
Hypersensitivity	0	0(0%)	0	0(0%)	0	1(1%)	1	1(<1%)	0·207
Grade 1	0	0(0%)	0	0(0%)	1	1(1%)	1	1(<1%)	0·207
Unsolicited adverse reactions within 0-28 days									
Any	15	11(5%)	19	15(7%)	10	9(8%)	44	35(6%)	0·515
Grade 1	3	2(1%)	5	3(1%)	3	3(3%)	11	8(1%)	0·427
Grade 2	12	10(5%)	14	12(6%)	7	7(6%)	33	29(5%)	0·752
Overall adverse reactions within 0-28 days									
Any	118	56(26%)	111	63(29%)	39	27(24%)	268	146(27%)	0·550
Grade 1	78	40(18%)	76	52(24%)	23	18(16%)	177	110(20%)	0·155
Grade 2	38	22(10%)	35	24(11%)	16	15(13%)	89	61(11%)	0·669
Grade 3	2	2(1%)	0	0(0%)	0	0(0%)	2	2(0%)	0·356

Abbreviation: alum, aluminum hydroxide

Note: n(%) represent the total number of participants who had adverse reactions (ie, adverse events related to vaccination).

* For differences across all groups.

Table 2-2 Adverse reactions reported within 28 days after the first dose of vaccine or alum only in phase 1 and phase 2

	1·5ug group (n=219)		3ug group (n=217)		Alum only group (n=114)		Total (n=550)		P value
	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)	
Solicited adverse reactions within 0-7 days									
Any	53	31(14%)	56	42(19%)	21	15(13%)	130	88(16%)	0·226
Grade 1	35	23(11%)	42	35(16%)	14	9(8%)	91	67(12%)	0·065
Grade 2	17	10(5%)	14	13(6%)	7	7(6%)	38	30(5%)	0·760
Grade 3	1	1(<1%)	0	0(0%)	0	0(0%)	1	1(<1%)	1·000
Injection site adverse reactions									
Pain	19	19(9%)	21	21(10%)	0	0(0%)	40	40(7%)	0·0003
Grade 1	18	18(8%)	21	21(10%)	0	0(0%)	39	39(7%)	0·0003
Grade 2	1	1(<1%)	0	0(0%)	0	0(0%)	1	1(<1%)	1·000
Swelling	1	1(<1%)	3	3(1%)	1	1(1%)	5	5(1%)	0·741
Grade 1	0	0(0%)	3	3(1%)	0	0(0%)	3	3(1%)	0·172
Grade 2	1	1(<1%)	0	0(0%)	1	1(1%)	2	2(<1%)	0·685
Induration	0	0(0%)	2	2(1%)	0	0(0%)	2	2(<1%)	0·198
Grade 1	0	0(0%)	2	2(1%)	0	0(0%)	2	2(<1%)	0·198
Pruritus	3	3(1%)	1	1(<1%)	0	0(0%)	4	4(1%)	0·540
Grade 1	3	3(1%)	1	1(<1%)	0	0(0%)	4	4(1%)	0·540
Systematic adverse reactions									
Fever	6	6(3%)	11	10(5%)	4	4(4%)	21	20(4%)	0·585
Grade 1	1	1(<1%)	2	2(1%)	2	2(2%)	5	5(1%)	0·363
Grade 2	4	4(2%)	9	8(4%)	2	2(2%)	15	14(3%)	0·441
Grade 3	1	1(<1%)	0	0(0%)	0	0(0%)	1	1(0%)	1·000
Cough	4	3(1%)	6	6(3%)	4	4(4%)	14	13(2%)	0·359
Grade 1	2	1(<1%)	3	3(1%)	2	2(2%)	7	6(1%)	0·516
Grade 2	2	2(1%)	3	3(1%)	2	2(2%)	7	7(1%)	0·797
Headache	5	4(2%)	2	2(1%)	3	3(3%)	10	9(2%)	0·464
Grade 1	2	2(1%)	2	2(1%)	1	1(1%)	5	5(1%)	1·000
Grade 2	3	3(1%)	0	0(0%)	2	2(2%)	5	5(1%)	0·158
Anorexia	3	2(1%)	2	2(1%)	2	2(2%)	7	6(1%)	0·755
Grade 1	1	1(<1%)	1	1(<1%)	2	2(2%)	4	4(1%)	0·343
Grade 2	2	2(1%)	1	1(<1%)	0	0(0%)	3	3(1%)	0·804
Diarrhoea	1	1(<1%)	2	2(1%)	4	3(3%)	7	6(1%)	0·182
Grade 1	1	1(<1%)	2	2(1%)	4	3(3%)	7	6(1%)	0·182
Nausea	3	2(1%)	2	2(1%)	2	2(2%)	7	6(1%)	0·755
Grade 1	3	2(1%)	2	2(1%)	2	2(2%)	7	6(1%)	0·755
Mucocutaneous eruption	1	1(<1%)	2	2(1%)	0	0(0%)	3	3(1%)	0·616
Grade 1	1	1(<1%)	1	1(<1%)	0	0(0%)	2	2(<1%)	1·000
Grade 2	0	0(0%)	1	1(<1%)	0	0(0%)	1	1(<1%)	0·602
Vomiting	1	1(<1%)	1	1(<1%)	0	0(0%)	2	2(<1%)	1·000
Grade 1	1	1(<1%)	1	1(<1%)	0	0(0%)	2	2(<1%)	1·000
Muscle pain	4	3(1%)	0	0(0%)	0	0(0%)	4	3(1%)	0·234
Grade 1	1	1(<1%)	0	0(0%)	0	0(0%)	1	1(<1%)	1·000
Grade 2	3	2(1%)	0	0(0%)	0	0(0%)	3	2(<1%)	0·356
Fatigue	2	1(<1%)	1	1(<1%)	1	1(1%)	4	3(1%)	1·000
Grade 1	1	1(<1%)	1	1(<1%)	1	1(1%)	3	3(1%)	1·000

Grade 2	1	1(<1%)	0	0(0%)	0	0(0%)	1	1(<1%)	1·000
Unsolicited adverse reactions within 0-28 days									
Any	7	6(3%)	17	13(6%)	7	7(6%)	31	26(5%)	0·190
Grade 1	2	1(<1%)	5	3(1%)	1	1(1%)	8	5(1%)	0·741
Grade 2	5	5(2%)	12	10(5%)	6	6(5%)	23	21(4%)	0·249
Overall adverse reactions within 0-28 days									
Any	60	33(15%)	73	46(21%)	28	19(17%)	161	98(18%)	0·239
Grade 1	37	23(11%)	47	36(17%)	15	10(9%)	99	69(13%)	0·069
Grade 2	22	13(6%)	26	18(8%)	13	12(11%)	61	43(8%)	0·316
Grade 3	1	1(<1%)	0	0(0)	0	0(0)	1	1(<1%)	1·000

Abbreviation: alum, aluminum hydroxide

Note: n(%) represent the total number of participants who had adverse reactions (ie, adverse events related to vaccination).

* For differences across all groups.

Table 2-3 Adverse reactions reported within 28 days after the second dose of vaccine or alum only in phase 1 and phase 2

	1·5ug group (n=214)		3ug group (n=211)		Alum only group (n=111)		Total (n=536)		P value
	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)	
Solicited adverse reactions within 0-7 days									
Any	50	31(14%)	36	25(12%)	8	8(7%)	94	64(12%)	0·153
Grade 1	40	27(13%)	29	22(10%)	6	6(5%)	75	55(10%)	0·115
Grade 2	9	7(3%)	7	7(3%)	2	2(2%)	18	16(3%)	0·847
Grade 3	1	1(<1%)	0	0(0%)	0	0(0%)	1	1(<1%)	1·000
Injection site adverse reactions									
Pain	25	25(12%)	20	20(9%)	2	2(2%)	47	47(9%)	0·0038
Grade 1	23	23(11%)	20	20(9%)	2	2(2%)	45	45(8%)	0·0078
Grade 2	2	2(1%)	0	0(0%)	0	0(0%)	2	2(<1%)	0·356
Swelling	2	2(1%)	4	4(2%)	0	0(0%)	6	6(1%)	0·272
Grade 1	0	0(0%)	1	1(<1%)	0	0(0%)	1	1(<1%)	0·601
Grade 2	2	2(1%)	3	3(1%)	0	0(0%)	5	5(1%)	0·541
Erythema	0	0(0%)	1	1(<1%)	0	0(0%)	1	1(<1%)	0·601
Grade 1	0	0(0%)	1	1(<1%)	0	0(0%)	1	1(<1%)	0·601
Pruritus	1	1(<1%)	1	1(<1%)	0	0(0%)	2	2(<1%)	1·000
Grade 1	1	1(<1%)	1	1(<1%)	0	0(0%)	2	2(<1%)	1·000
Systematic adverse reactions									
Fever	3	3(1%)	2	2(1%)	1	1(1%)	6	6(1%)	1·000
Grade 1	2	2(1%)	0	0(0%)	0	0(0%)	2	2(<1%)	0·356
Grade 2	0	0(0%)	2	2(1%)	1	1(1%)	3	3(1%)	0·330
Grade 3	1	1(<1%)	0	0(<1%)	0	0(0%)	1	1(<1%)	1·000
Cough	4	3(1%)	2	2(1%)	1	1(1%)	7	6(1%)	1·000
Grade 1	2	1(<1%)	1	1(<1%)	1	1(1%)	4	3(1%)	1·000
Grade 2	2	2(1%)	1	1(<1%)	0	0(0%)	3	3(1%)	0·804
Headache	4	3(1%)	3	2(1%)	0	0(0%)	7	5(1%)	0·640
Grade 1	3	2(1%)	2	1(<1%)	0	0(0%)	5	3(1%)	0·804
Grade 2	1	1(<1%)	1	1(<1%)	0	0(0%)	2	2(<1%)	1·000
Anorexia	2	2(1%)	2	2(1%)	0	0(0%)	4	4(1%)	0·688
Grade 1	1	1(<1%)	2	2(1%)	0	0(0%)	3	3(1%)	0·615
Grade 2	1	1(<1%)	0	0(0%)	0	0(0%)	1	1(<1%)	1·000
Diarrhoea	1	1(<1%)	0	0(0%)	1	1(1%)	2	2(<1%)	0·685
Grade 1	1	1(<1%)	0	0(0%)	1	1(1%)	2	2(<1%)	0·685
Nausea	2	2(1%)	1	1(<1%)	0	0(0%)	3	3(1%)	0·804
Grade 1	2	2(1%)	1	1(<1%)	0	0(0%)	3	3(1%)	0·804
Mucocutaneous eruption	1	1(<1%)	0	0(0%)	1	1(1%)	2	2(<1%)	0·685
Grade 2	1	1(<1%)	0	0(0%)	1	1(1%)	2	2(<1%)	0·685
Vomiting	2	2(1%)	0	0(0%)	1	1(1%)	3	3(1%)	0·429
Grade 1	2	2(1%)	0	0(0%)	1	1(1%)	3	3(1%)	0·429
Muscle pain	1	1(<1%)	0	0(0%)	0	0(0%)	1	1(<1%)	1·000
Grade 1	1	1(<1%)	0	0(0%)	0	0(0%)	1	1(<1%)	1·000
Fatigue	2	1(<1%)	0	0(0%)	0	0(0%)	2	1(<1%)	1·000
Grade 1	2	1(<1%)	0	0(0%)	0	0(0%)	2	1(<1%)	1·000
Hypersensitivity	0	0(0%)	0	0(0%)	1	1(1%)	1	1(<1%)	0·207

Grade 1	0	0(0%)	0	0(0%)	1	1(1%)	1	1(<1%)	0·207
Unsolicited adverse reactions within 0-28 days									
Any	8	6(3%)	2	2(1%)	3	3(3%)	13	11(2%)	0·351
Grade 1	1	1(<1%)	0	0(0%)	2	2(2%)	3	3(1%)	0·110
Grade 2	7	5(2%)	2	2(1%)	1	1(1%)	10	8(1%)	0·584
Overall adverse reactions within 0-28 days									
Any	58	35(16%)	38	26(12%)	11	11(10%)	107	72(13%)	0·240
Grade 1	41	28(13%)	29	22(10%)	8	8(7%)	78	58(11%)	0·283
Grade 2	16	10(5%)	9	9(4%)	3	3(3%)	28	22(4%)	0·784
Grade 3	1	1(<1%)	0	0(0)	0	0(0)	1	1(<1%)	1·000

Abbreviation: alum, aluminum hydroxide

Note: n(%) represent the total number of participants who had adverse reactions (ie, adverse events related to vaccination).

* For differences across all groups.

Table 2-4 Adverse reactions reported within 28 days after first and second doses of vaccine or alum only in different age groups in phase 1 and phase 2

	3-5 years				6-11 years				12-17 years			
	1.5ug group (n=57)	3ug group (n=56)	Alum only group (n=30)	P value	1.5ug group (n=81)	3ug group (n=81)	Alum only group (n=42)	P value	1.5ug group (n=81)	3ug group (n=80)	Alum only group (n=42)	P value
Solicited adverse reactions within 0-7 days												
Any	12(21%)	14(25%)	7(23%)	0·874	11(14%)	15(19%)	6(14%)	0·680	28(35%)	30(38%)	9(21%)	0·186
Grade 1	7(12%)	8(14%)	3(10%)	0·899	7(9%)	13(16%)	5(12%)	0·343	25(31%)	30(38%)	7(17%)	0·056
Grade 2	4(7%)	9(16%)	5(17%)	0·251	4(5%)	6(7%)	2(5%)	0·802	8(10%)	4(5%)	2(5%)	0·485
Grade 3	1(2%)	0(0%)	0(0%)	1·000	1(1%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	0(0%)	1·000
Injection site adverse reactions												
Pain	6(11%)	4(7%)	0(0%)	0·203	5(6%)	10(12%)	1(2%)	0·136	25(31%)	21(26%)	1(2%)	0·0003
Grade 1	6(11%)	4(7%)	0(0%)	0·203	5(6%)	10(12%)	1(2%)	0·136	23(28%)	21(26%)	1(2%)	0·0005
Grade 2	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	0(0%)	1·000	2(2%)	0(0%)	0(0%)	0·354
Swelling	0(0%)	2(4%)	0(0%)	0·195	0(0%)	1(1%)	0(0%)	1·000	3(4%)	3(4%)	1(2%)	1·000
Grade 1	0(0%)	2(4%)	0(0%)	0·195	0(0%)	0(0%)	0(0%)	1·000	0(0%)	2(3%)	0(0%)	0·196
Grade 2	0(0%)	0(0%)	0(0%)	1·000	0(0%)	1(1%)	0(0%)	1·000	3(4%)	2(3%)	1(2%)	1·000
Induration	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	0(0%)	1·000	0(0%)	2(3%)	0(0%)	0·196
Grade 1	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	0(0%)	1·000	0(0%)	2(3%)	0(0%)	0·196
Erythema	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	0(0%)	1·000	0(0%)	1(1%)	0(0%)	0·601
Grade 1	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	0(0%)	1·000	0(0%)	1(1%)	0(0%)	0·601
Pruritus	0(0%)	1(2%)	0(0%)	0·601	1(1%)	0(0%)	0(0%)	1·000	2(2%)	1(1%)	0(0%)	0·802
Grade 1	0(0%)	1(2%)	0(0%)	0·601	1(1%)	0(0%)	0(0%)	1·000	2(2%)	1(1%)	0(0%)	0·802
Systematic adverse reactions												
Fever	5(9%)	5(9%)	3(10%)	1·000	3(4%)	4(5%)	2(5%)	1·000	1(1%)	2(3%)	0(0%)	0·613
Grade 1	1(2%)	0(0%)	1(3%)	0·686	1(1%)	1(1%)	1(2%)	1·000	1(1%)	1(1%)	0(0%)	1·000

	3-5 years				6-11 years				12-17 years			
	1.5ug group (n=57)	**3ug group (n=56)**	**Alum only group (n=30)**	**P value**	**1.5ug group (n=81)**	**3ug group (n=81)**	**Alum only group (n=42)**	**P value**	**1.5ug group (n=81)**	**3ug group (n=80)**	**Alum only group (n=42)**	**P value**
Grade 2	3(5%)	5(9%)	2(7%)	0·841	1(1%)	4(5%)	1(2%)	0·447	0(0%)	1(1%)	0(0%)	0·601
Grade 3	1(2%)	0(0%)	0(0%)	1·000	1(1%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	0(0%)	1·000
Cough	1(2%)	3(5%)	2(7%)	0·506	2(2%)	2(2%)	2(5%)	0·750	2(2%)	3(4%)	1(2%)	0·875
Grade 1	0(0%)	0(0%)	1(3%)	0·210	0(0%)	1(1%)	1(2%)	0·683	1(1%)	3(4%)	1(2%)	0·738
Grade 2	1(2%)	3(5%)	1(3%)	0·735	2(2%)	1(1%)	1(2%)	1·000	1(1%)	0(0%)	0(0%)	1·000
Headache	0(0%)	0(0%)	1(3%)	0·210	2(2%)	0(0%)	0(0%)	0·355	4(5%)	4(5%)	2(5%)	1·000
Grade 1	0(0%)	0(0%)	0(0%)	1·000	1(1%)	0(0%)	0(0%)	1·000	2(2%)	3(4%)	1(2%)	0·875
Grade 2	0(0%)	0(0%)	1(3%)	0·210	1(1%)	0(0%)	0(0%)	1·000	3(4%)	1(1%)	1(2%)	0·843
Anorexia	0(0%)	1(2%)	1(3%)	0·517	1(1%)	0(0%)	0(0%)	1·000	2(2%)	3(4%)	1(2%)	0·875
Grade 1	0(0%)	0(0%)	1(3%)	0·210	0(0%)	0(0%)	0(0%)	1·000	1(1%)	3(4%)	1(2%)	0·738
Grade 2	0(0%)	1(2%)	0(0%)	0·601	1(1%)	0(0%)	0(0%)	1·000	2(2%)	0(0%)	0(0%)	0·354
Diarrhoea	0(0%)	1(2%)	2(7%)	0·060	0(0%)	1(1%)	1(2%)	0·683	2(2%)	0(0%)	1(2%)	0·427
Grade 1	0(0%)	1(2%)	2(7%)	0·060	0(0%)	1(1%)	1(2%)	0·683	2(2%)	0(0%)	1(2%)	0·427
Nausea	1(2%)	1(2%)	1(3%)	1·000	0(0%)	0(0%)	0(0%)	1·000	2(2%)	1(1%)	1(2%)	1·000
Grade 1	1(2%)	1(2%)	1(3%)	1·000	0(0%)	0(0%)	0(0%)	1·000	2(2%)	1(1%)	1(2%)	1·000
Mucocutaneous eruption	0(0%)	0(0%)	1(3%)	0·210	2(2%)	0(0%)	0(0%)	0·355	0(0%)	2(3%)	0(0%)	0·196
Grade 1	0(0%)	0(0%)	0(0%)	1·000	1(1%)	0(0%)	0(0%)	1·000	0(0%)	1(1%)	0(0%)	0·601
Grade 2	0(0%)	0(0%)	1(3%)	0·210	1(1%)	0(0%)	0(0%)	1·000	0(0%)	1(1%)	0(0%)	0·601
Vomiting	1(2%)	1(2%)	0(0%)	1·000	0(0%)	0(0%)	1(2%)	0·206	2(2%)	0(0%)	0(0%)	0·354
Grade 1	1(2%)	1(2%)	0(0%)	1·000	0(0%)	0(0%)	1(2%)	0·206	2(2%)	0(0%)	0(0%)	0·354
Muscle pain	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	0(0%)	1·000	4(5%)	0(0%)	0(0%)	0·076

	3-5 years				6-11 years				12-17 years			
	1.5ug group (n=57)	3ug group (n=56)	Alum only group (n=30)	P value	1.5ug group (n=81)	3ug group (n=81)	Alum only group (n=42)	P value	1.5ug group (n=81)	3ug group (n=80)	Alum only group (n=42)	P value
Grade 1	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	0(0%)	1·000	2(2%)	0(0%)	0(0%)	0·354
Grade 2	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	0(0%)	1·000	2(2%)	0(0%)	0(0%)	0·354
Fatigue	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	1(2%)	0·206	1(1%)	1(1%)	0(0%)	1·000
Grade 1	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	1(2%)	0·206	1(1%)	1(1%)	0(0%)	1·000
Grade 2	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	1(2%)	0·206	1(1%)	0(0%)	0(0%)	1·000
Hypersensitivity	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	1(2%)	0·207
Grade 1	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	1(2%)	0·207
Unsolicited adverse reactions within 0-28 days												
Any	2(4%)	6(11%)	3(10%)	0·306	2(2%)	5(6%)	3(7%)	0·443	7(9%)	4(5%)	3(7%)	0·677
Grade 1	0(0%)	1(2%)	1(3%)	0·517	0(0%)	1(1%)	1(2%)	0·683	2(2%)	1(1%)	1(2%)	1·000
Grade 2	2(4%)	5(9%)	3(10%)	0·403	2(2%)	4(5%)	2(5%)	0·719	6(7%)	3(4%)	2(5%)	0·623
Overall adverse reactions within 0-28 days												
Any	13(23%)	15(27%)	9(30%)	0·754	12(15%)	18(22%)	7(17%)	0·461	31(38%)	30(38%)	11(26%)	0·383
Grade 1	7(12%)	8(14%)	4(13%)	0·950	7(9%)	14(17%)	6(14%)	0·269	26(32%)	30(38%)	8(19%)	0·110
Grade 2	5(9%)	10(18%)	7(23%)	0·145	6(7%)	9(11%)	4(10%)	0·743	11(14%)	5(6%)	4(10%)	0·300
Grade 3	1(2%)	0(0%)	0(0%)	1·000	1(1%)	0(0%)	0(0%)	1·000	0(0%)	0(0%)	0(0%)	1·000

Abbreviation: alum, aluminum hydroxide

Note: Data are n(%), representing the total number of participants who had adverse reactions (ie, adverse events related to vaccination).

Appendix 3 Clinically significant laboratory abnormalities

Table 3-1 Clinically significant laboratory abnormalities at day 3 after the first dose and second dose

Dose	Laboratory index	1·5ug group	3ug group	Alum only group	Total
First dose	**N**	**27**	**26**	**18**	**71**
	White blood cells				
	Grade 1	0(0)	2(8%)	0(0)	2(3%)
Second dose	**N**	**27**	**26**	**16**	**69**
	White blood cells				
	Grade 1	1(4%)	0(0)	0(0)	1(1%)
	Hemoglobin				
	Grade 1	0(0)	1(4%)	0(0)	1(1%)

Abbreviation: alum, aluminum hydroxide

Note: Data are n(%), representing the total number of participants who had clinically significant laboratory abnormalities.

Appendix 4 Immunogenicity results

Table 4-1 Immunogenicity results of neutralising antibody to live SARS-CoV-2 induced by CoronaVac in phase 1

Time	Characteristics	1·5ug group (N=27)	3ug group (N=26)	Alum only group (N=16)	*P* value_ three group	*P* value_ 1.5ug vs 3ug	Difference/ Ratio * 95%CI
Before vaccination	Seropositive n(%)	0 (0·0)	0 (0·0)	0 (0·0)	1·000	1·000	0·0
	(95%CI)	(0·0-12·8)	(0·0-13·2)	(0·0-20·6)			(-12·7-13·1)
	GMT	2·0	2·0	2·0	NA	NA	1·0
	(95%CI)	(2·0-2·0)	(2·0-2·0)	(2·0-2·0)			(1·0-1·0)
28 days after Dose 1	Seropositive n(%)	16 (59·3)	21 (80·8)	0 (0·0)	<0·0001	0·088	-21.5
	(95%CI)	(38·8-77·6)	(60·7-93·5)	(0·0-20·6)			(-45·5-2·4)
	Seroconversion n(%)	16 (59·3)	21 (80·8)	0 (0·0)	<0·0001	0·088	-21·5
	(95%CI)	(38·8-77·6)	(60·7-93·5)	(0·0-20·6)			(-45·5-2·4)
	GMT	8·0	14·1	2·0	<0·0001	0·015	0·6
	(95%CI)	(5·6-11·4)	(10·4-19·0)	(2·0-2·0)			(0·4-0·9)
	GMI	4·0	7·0	1·0	<0·0001	0·015	0·6
	(95%CI)	(2·8-5·7)	(5·2-9·5)	(1·0-1·0)			(0·4-0·9)
28 days after Dose 2	Seropositive n(%)	27 (100·0)	26 (100·0)	0 (0·0)	<0·0001	1·000	0·0
	(95%CI)	(87·2-100·0)	(86·8-100·0)	(0·0-20·6)			(-12·7-13·1)
	Seroconversion n(%)	27 (100·0)	26 (100·0)	0 (0·0)	<0·0001	1·000	0·0
	(95%CI)	(87·2-100·0)	(86·8-100·0)	(0·0-20·6)			(-12·7-13·1)
	GMT	55·0	117·4	2·0	<0·0001	0·0012	0·5
	(95%CI)	(38·9-77·9)	(87·8-157·0)	(2·0-2·0)			(0·3-0·7)
	GMI	27·5	58·7	1·0	<0·0001	0·0012	0·5
	(95%CI)	(19·4-39·0)	(43·9-78·5)	(1·0-1·0)			(0·3-0·7)

Abbreviation: alum, aluminum hydroxide

* The differences refer to the differences of seroconversion rate or seropositive rate (1.5ug group - 3ug group); The ratios refer to the ratios of GMT or GMI (1.5ug group/3ug group).

Table 4-2 Immunogenicity results of neutralising antibody to live SARS-CoV-2 induced by CoronaVac in phase 2

Time	Characteristics	1·5ug group （N=186）	3ug group （N=180）	Alum only group （N=94）	*P* value_ three group	*P* value_ 1·5ug vs 3ug	Difference/ Ratio * 95%CI
Before vaccination	Seropositive n(%) (95%CI)	0 (0·0) (0·0-2·0)	0 (0·0) (0·0-2·0)	0 (0·0) (0·0-3·9)	1·000	1·000	0·0 (-2·0-2·1)
	GMT (95%CI)	2·0 (2·0-2·0)	2·0 (2·0-2·0)	2·0 (2·0-2·0)	NA	NA	1·0 (1·0-1·0)
28 days after Dose 2	Seropositive n(%) (95%CI)	180 (96·8) (93·1-98·8)	180 (100·0) (98·0-100·0)	0 (0.0) (0·0-3·9)	<0·0001	0·030	-3·2 (-5·8 - -0·7)
	Seroconversion n(%) (95%CI)	180 (96·8) (93·1-98·8)	180 (100·0) (98·0-100·0)	0 (0.0) (0·0-3·9)	<0·0001	0·030	-3·2 (-5·8 - -0·7)
	GMT (95%CI)	86·4 (73·9-101·0)	142·2 (124·7-162·1)	2·0 (2·0-2·1)	<0·0001	<0·0001	0·6 (0·5-0.7)
	GMI (95%CI)	43·2 (36·9-50·5)	71·1 (62·4-81·1)	1·0 (1·0-1·0)	<0·0001	<0·0001	0·6 (0·5-0.7)

Abbreviation: alum, aluminum hydroxide

* The differences refer to the differences of seroconversion rate or seropositive rate (1.5ug group - 3ug group); The ratios refer to the ratios of GMT or GMI (1.5ug group/3ug group).

Table 4-3 Comparisons of seroconversion rates and GMTs of neutralising antibodies to live SARS-CoV-2 in different age groups at day 28 after the second dose

Doses	Characteristics	Phase 1				Phase 2			
		3-5 years	6-11 years	12-17 years	P value	3-5 years	6-11 years	12-17 years	P value
1·5ug group	Seroconversion n (%)	9(100·0)	9(100·0)	9(100·0)	1·000	46 (100·0)	68 (98·6)	66 (93·0)	0·140
	(95%CI)	(66·4-100·0)	(66·4-100·00)	(66·4-100·0)		(92·3-100·0)	(92·2-99·96)	(84·3-97·7)	
	GMT	71·9	50·5	45·9	0·540	94·1	90·3	78·3	0·612
	(95%CI)	(38·0-136·0)	(30·9-82·6)	(19·2-109·8)		(71·2, 124·2)	(72·6-112·2)	(57·5-106·6)	
3ug group	Seroconversion n (%)	9(100·0)	9(100·0)	8(100·0)	1·000	45 (100·0)	68 (100·0)	67 (100·0)	1·000
	(95%CI)	(66·4-100·0)	(66·4-100·0)	(63·1-100·0)		(92·1-100·0)	(94·7-100·0)	(94·6-100·0)	
	GMT	212·6	101·6	70·8	**0·0020**	140·5	139·7	146·0	0·954
	(95%CI)	(132·2-342·1)	(64·0-161·2)	(47·5-105·7)		(113·4-174·0)	(112·7-173·1)	(114·2-186·8)	

Appendix 5 Serious adverse events

As of June 12, 2021, only one serious adverse event has been reported, which was considered unrelated to vaccination. The case narrative of this serious adverse events as follows:

A 5-year-old boy received the first dose of investigational vaccine on Nov 23, 2020 and received the second dose on Dec 21, 2020. On Dec 30 2020, he had cough, expectoration and fever of 37.5°C, and the symptoms did not improve after oral drug treatment. The subject was then hospitalized on Jan 2, 2021. During hospitalization, he had blood tests and chest X-ray test: WBC.10.46$^{10\hat{}9\hat{}/L}$, NEUT%61.70%, LYMPH%27.40%, RBC5.06$^{10\hat{}12/L}$, PLT310.00$^{10\hat{}9/L}$, CRP<5mg/L, hs-CRP l.30mg/L, and X-ray indicated pneumonia in right lower lobe. After admission, he was given anti-infection (Cefotaxime), and cough and phlegm treatment (Ambroxol injection). He recovered and discharged on Jan 11, 2021.

Causality: According to the subject's symptoms and related examinations, the serious adverse event was clearly diagnosed as "pneumonia". It was effective after symptomatic treatment. In addition, the inactivated vaccine did not cause infectious diseases. Therefore, this serious adverse event was considered possibly unrelated to vaccination.