Supplemental Information for

Gut microbiota composition is associated with SARS-CoV-2 vaccine immunogenicity and adverse events

This file includes:
Supplementary methods
Supplementary figures 1 to 9
Supplementary tables 1 to 11
Supplementary references

Supplementary methods

Serological tests

For the SARS-CoV-2 surrogate virus neutralization test (sVNT), 10ul of plasma was diluted at 1:10 for CoronaVac and 1:200 for BNT162b2 and mixed with an equal volume of horseradish peroxidase (HRP) conjugated to SARS-CoV-2 spike receptor binding domain (RBD) (6 ng). After incubation for 30 min at 37°C, a 100-µl volume of each mixture was added to each well on the microtiter plate coated with ACE-2 receptor. The plate was sealed and incubated at room temperature for 15 min at 37°C. The plate was then washed with wash solution and 100µl of 3,3',5,5'- tetramethylbenzidine (TMB) solution was added to each well and incubated in the dark at room temperature for 15 min. The reaction was stopped by addition of 50 µl of Stop Solution to each well and the absorbance read at 450 nm in an ELISA microplate reader. The assay validity was based on values representing optical density at 450 nm (OD_{450}) for positive and negative results falling within the range of recommended values. On the basis of the assumption that the positive and negative controls gave the recommended OD450 values, percentage of inhibition of each plasma was calculated as follows: Inhibition (%) = (1 - sample OD value/negative-control OD value) x 100. Inhibition values of >20% are regarded as positive[1,2].

For SARS-CoV-2 spike RBD IgG ELISA, 96-well plates (Nunc MaxiSorp; Thermo Fisher Scientific) were coated overnight with 100 ng per well of the purified recombinant RBD protein in phosphate-buffered saline (PBS) buffer. The plates were then blocked with 100 µl of ChonBlock blocking/sample dilution ELISA buffer (Chondrex Inc., Redmond, WA, USA) and incubated at room temperature for 2 h. Each plasma sample was tested from the dilution of 1:100 to 1:12800 in ChonBlock blocking/sample dilution ELISA buffer and added to the

ELISA wells of each plate for 2 h of incubation at 37°C. After extensive washing with PBS containing 0.1% Tween 20, horseradish peroxidase (HRP)-conjugated goat anti-human IgG (Thermo Fisher Scientific, Catalog No. A18805) (1:5,000) was added for 1 h at 37°C. The ELISA plates were then washed five times with PBS containing 0.1% Tween 20. Subsequently, 100 µl of HRP substrate (Ncm TMB One; New Cell and Molecular Biotech Co. Ltd., Suzhou, China) was added into each well. After 15 min of incubation, the reaction was stopped by adding 50 µl of 2 M H_2SO_4 solution and analyzed on an absorbance microplate reader at 450-nm wavelength. The validation and optical density cut-off for a positive result were as described in the previous publication[1,2]. The area under the curve (AUC) of each sample was calculated by GraphPad software.

DNA extraction and sequencing library construction

Fecal DNA was extracted from the pellet using Maxwell RSC PureFood GMO and Authentication Kit (Promega, Madison, WI). Briefly, the fecal pellet was added to 1 mL of CTAB buffer and vortexed for 30 seconds, then the sample was heated at 95°C for 5 minutes. After that, the samples were vortexed thoroughly with beads at maximum speed for 15 minutes. Then, 40 µL of proteinase K and 20 µL of RNase A was added to the sample and the mixture was incubated at 70°C for 10 minutes. The supernatant was then obtained by centrifuging at 13,000*g* for 5 minutes and was added into the Maxwell RSC machine for DNA extraction. Extracted DNA was subject to DNA libraries construction, completed through the processes of end repairing, adding A to tails, purification and PCR amplification, using Nextera DNA Flex Library Preparation kit (Illumina, San Diego, CA)[3,4].

Sequence data processing and analysis

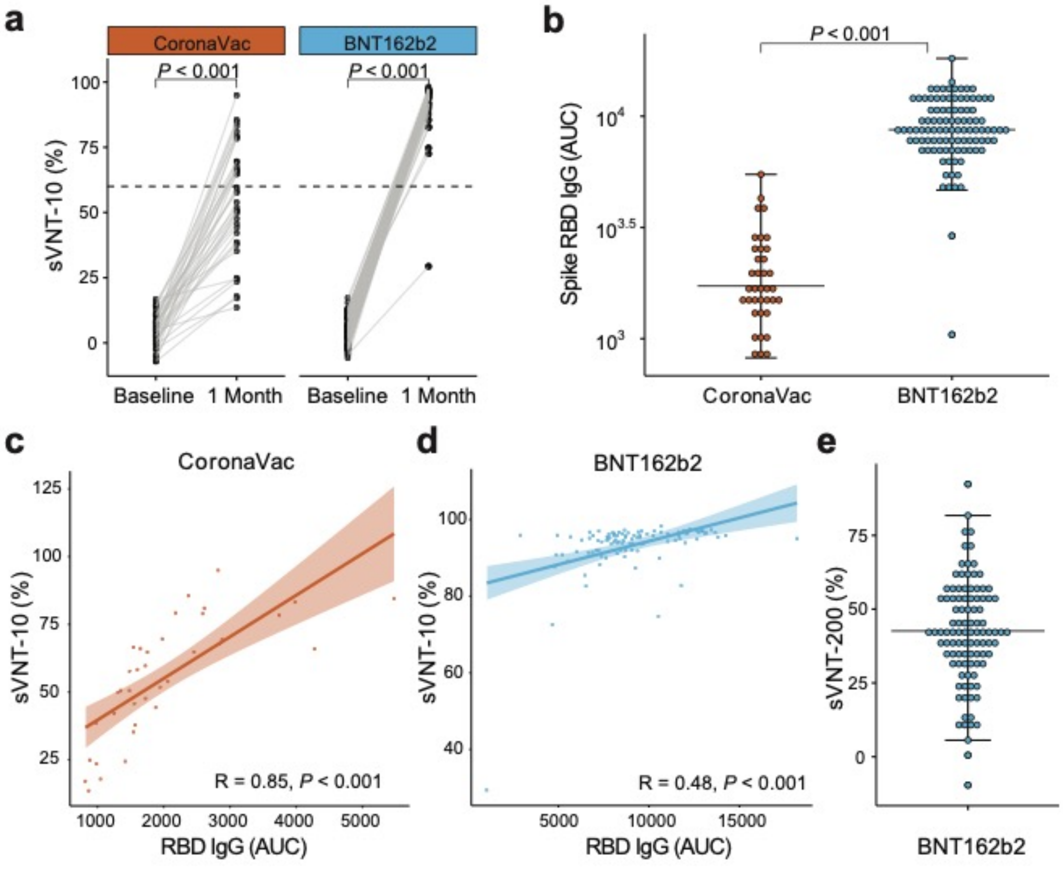
Raw reads were quality filtered and trimmed using KneadData v0.10.0 with Trimmomatic v0.39 to remove adaptor and low-quality sequences (Parametersetting: "MINLEN:50 ILLUMINACLIP:TruSeq3-PE.fa:2:40:15 SLIDINGWINDOW:4:20") and with Bowtie2 (Parameter settings: "--very-sensitive –dovetail") to remove human host DNA by mapping reads onto human reference genome GRCh38. We acquired 2096.78 Gb high-quality pairedend reads for the 272 samples with an average of 7.71 Gb per sample. Following this, microbiota taxonomic compositions and functional potentials (including functional pathways and Gene Ontologies) were inferred from quality-filtered reads using MetaPhlAn (v3.0) and HUMAnN (v3.0), respectively, with default settings. Beta diversity (between-sample diversity) was calculated as Jensen-Shannon Divergence (JSD) index by the phyloseq and vegan packages and visualized by non-metric multidimensional scaling (NMDS). Alpha diversity (within-sample diversity) indices, including observed species, Shannon and Simpson index, were calculated on the basis of the species profile for each sample. Gut microbial motility was calculated based on species relative abundance and motility phenotype (the GOLD database (v202109) and the International Journal of Systematic and Evolutionary Microbiology (IJSEM) database), per Guittar *et al*[5].

Statistical methods

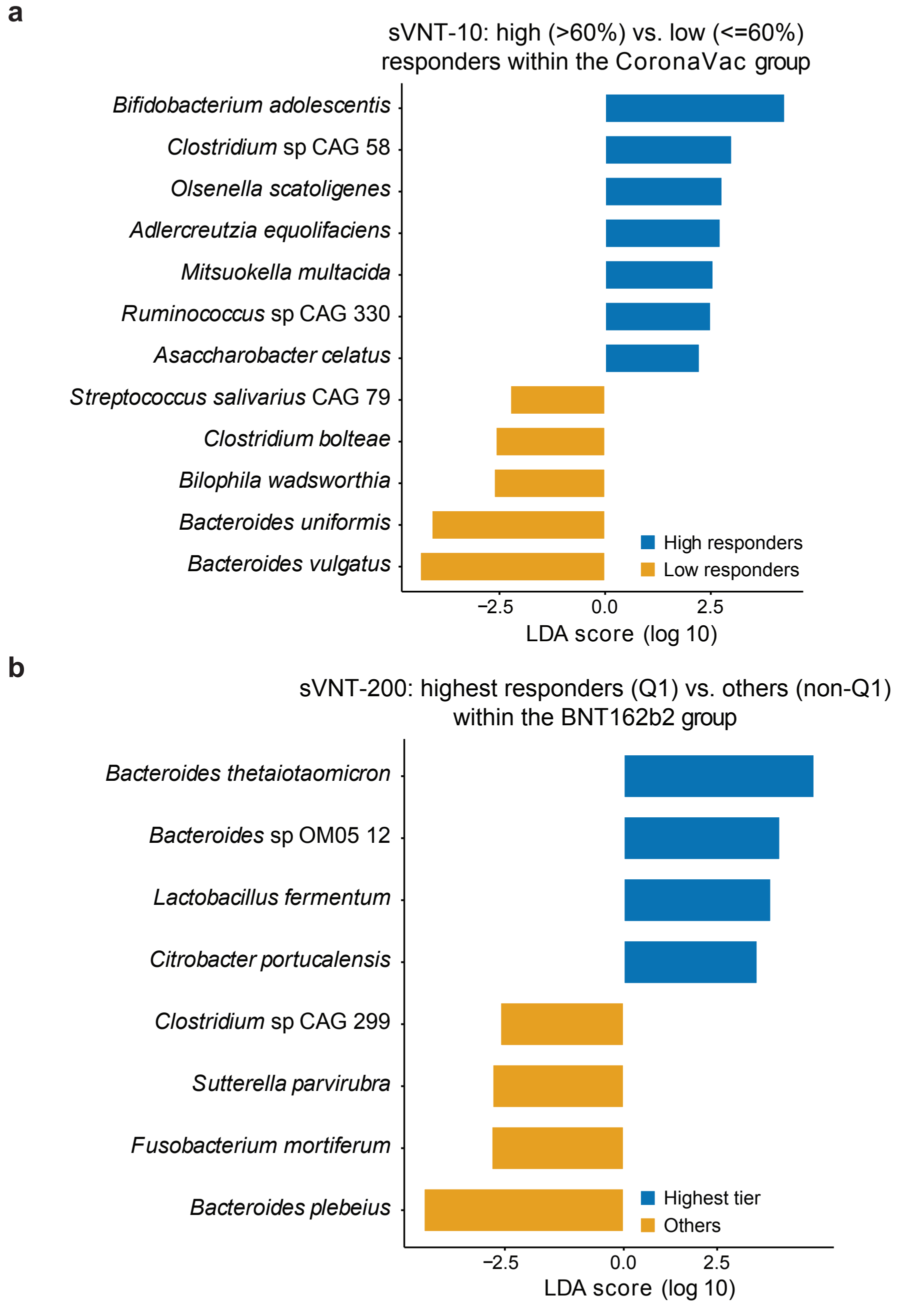
Baseline characteristics and adverse events after the first and second dose of each vaccination group were compared using Fisher's exact test for the categorical variables and Wilcoxon rank-sum test for continuous variables. The comparisons of immunity markers between two types of vaccines were further adjusted for potential confounders such as age and comorbidities using adjusted linear regression and propensity score matching analysis. Pairwise multilevel comparisons among baseline and one-month samples of BNT162b2 and CoronaVac vaccinees were carried out on the JSD distance matrix using pairwise Adonis test. Associations between gut microbial community composition and patients' characteristics were assessed using permutational multivariate analysis of variance (PERMANOVA). Unsupervised clustering was conducted using the partitioning around medoids (PAM) clustering method based on the JSD distance matrix, and the number of clusters was determined according to the Calinski-Harabasz index, Silhouette coefficient and sample sizes. Paired Wilcoxon rank-sum tests (two-sides) were performed to compare the α-diversity of baseline and one-month samples within each vaccine group. Differentially abundant species between groups/clusters were identified using the linear discriminant analysis effect size (LEfSe v1.1.01) (linear discriminant analysis (LDA) score > 2, and $P < 0.05$). Correlations between continuous variables, including immune responses (sVNT%, spike RBD IgG level, species abundance and function abundance) were analyzed using Spearman's correlation tests, while the immune response differences amongst other binary/categorical variables were tested by Wilcoxon rank-sum tests. In the correlation analysis between the sVNT% and relative abundances of selected bacterial species maerkers, partial Spearman correlations were used to adjust for confounding factors. Generalized linear models (GLM) for binominal outcomes (high-responders versus low-responders or highest-tier responders vs others) with receiver operating characteristic (ROC) curve was applied to determine the prediction value of the identified biomarkers. GLMs were also constructed to investigate modification effects while adjusting for potential confounders identified in univariable analysis. Mixed effect models were built to identify persistently differentially abundant species, using *lme* (of the nlme package) or *lme.zig* (of the NBZIMM package) that was optimized for zero-inflated microbiome data[6], where appropriate. *P* values less than 0.05 were considered statistically significant. FDR corrected *P* values were generated in relevant statistical tests such as correlation analysis between selected bacterial species markers and correlation analysis between fimbriae/flagella-related gene ontology abundance and bacterial relative abundance in which multiple-testing was applicable. FDR correction was not applied in LEfSe analysis because it first detected potential bacteria markers by non-parametric factorial Kruskal-Wallis (KW) test and Wilcoxon sum-rank test followed by LDA of significantly differentially abundant markers[7]. Since LDA is a multivariable analysis, we did not adjust for *P* values[8]. Other analyses in which FDR correction was not applicable included binary analysis of demographics, correlation between two antibody markers and mixed modeling for longitudinal differential abundant of selected bacteria markers because they did not include multiple-testing and/or they were based on *a priori* hypotheses. All the analyses and data visualization were performed in R V4.0.3 with the following packages: phyloseq, vegan, tidyverse, dplyr, glm, ppcor, pairwise.adonis, pROC. NBZIMM, ggplot2, ggpubr, ComplexHeatmap, circlize and Hmisc.

Supplementary figures

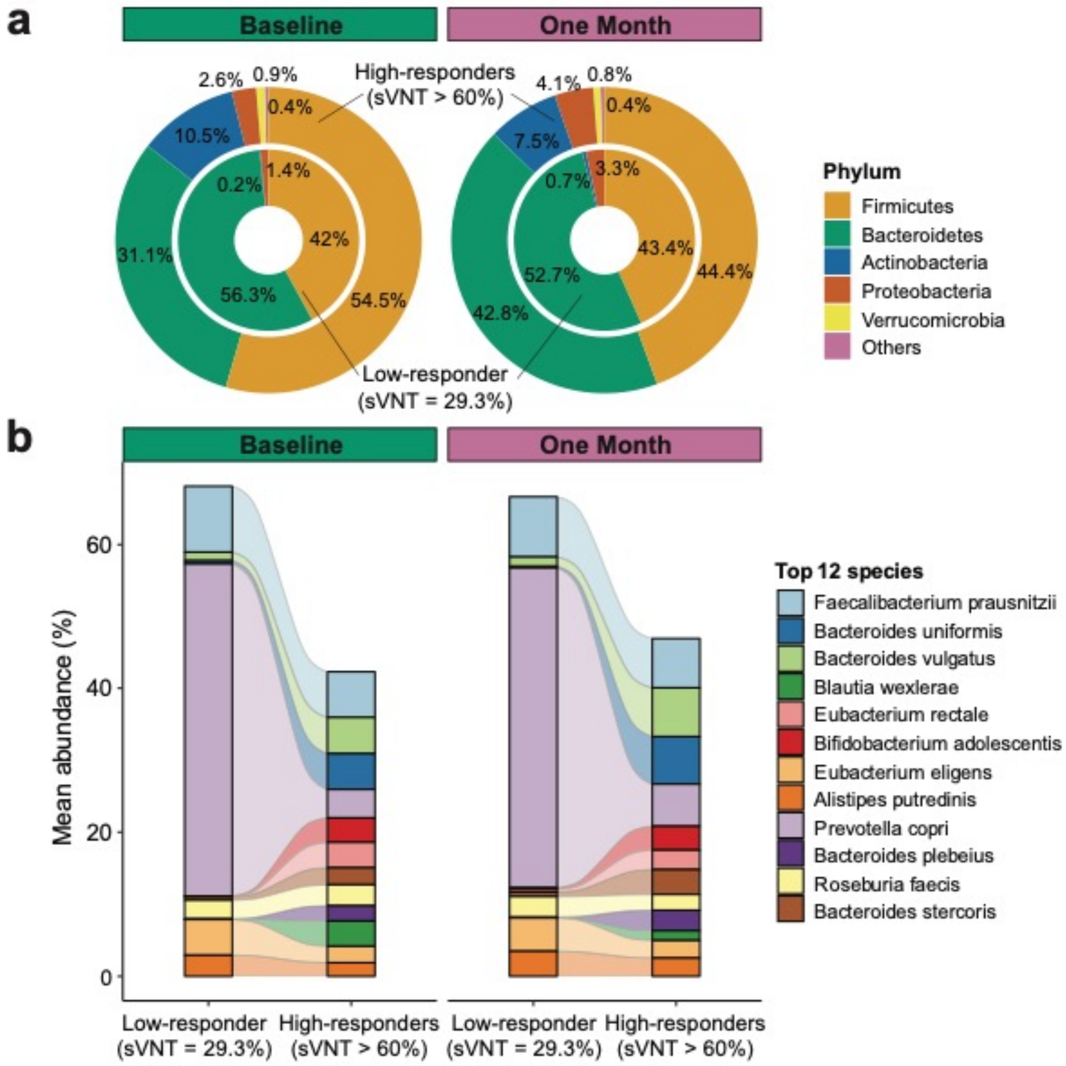
Supplementary Figure 1. Immune response against SARS-CoV-2 in the study cohort. a, sVNT level (%) to SARS-CoV-2 (10-fold dilution) at baseline and at one month after second dose of vaccination for CoronaVac (n = 37) and BNT162b2 (n = 101). Dashed line indicates sVNT = 60%. *P* values were given by paired Wilcoxon rank-sum test (two-sided). **b**, spike RBD IgG titre (AUC) at baseline and at one month after second dose of vaccination for CoronaVac (n = 37) and BNT162b2 (n = 101). *P* values were given by Wilcoxon rank-sum test (two-sided). **c**, Correlation between sVNT-10 (%) and spike RBD IgG titre at one month in CoronaVac vaccinees (n = 37). **d**, Correlation between sVNT-200 (%) and spike RBD IgG titre at one month in BNT162b2 vaccinees (n = 101). **e**, sVNT-200 (%) at one month after second dose of vaccination in BNT162b2 vaccinees (n = 101). sVNT-10: sVNT level of 10-fold diluted plasma; sVNT-200: sVNT level of 200-fold diluted plasma. Elements on dot plots: center line, median; whiskers, 1.5x interquartile range; points, outliers. Correlation between sVNT data and spike RBD IgG titre (AUC) were examined using Spearman's correlation test. Regression lines with 95% CI (shaded area) were shown on scatter plots.



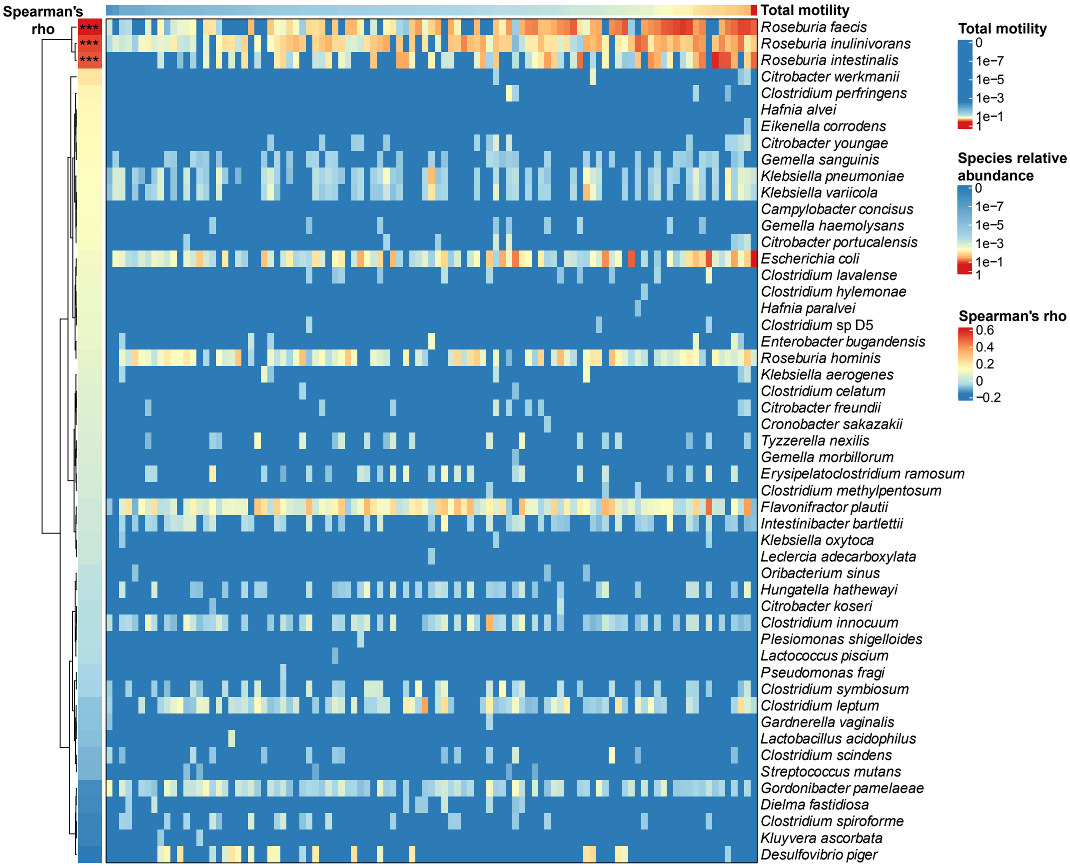
Supplementary Figure 2. Gut microbiota species at one month after second dose of vaccination enriched in high-responders. a, Gut bacterial species encirched in high-responders of CoronaVac vaccine (n = 36). **b,** Gut bacterial species encirched in high-respnders of BNT162b2 vaccine (n = 98). Differential gut bacterial species were detected by LEfSe. sVNT-10: sVNT level of 10-fold diluted plasma; sVNT-200: sVNT level of 200-fold diluted plasma.



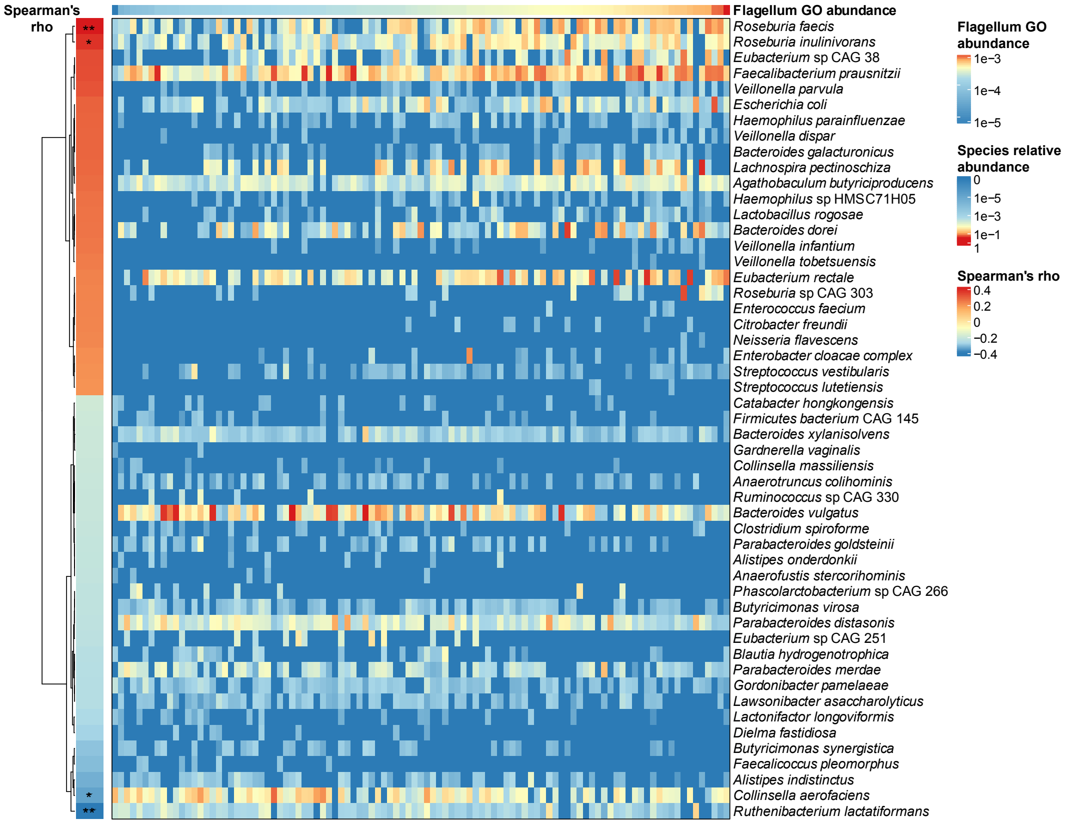
Supplementary Figure 3. Gut microbiota dysbiosis in the subject with very low level of sVNT (10-fold dilution) against BNT162b2 vaccine at **a**, phylum and **b**, species levels. Inner and outer circles in a represent BNT162b2 low-responder and others (n = 100), respectively.



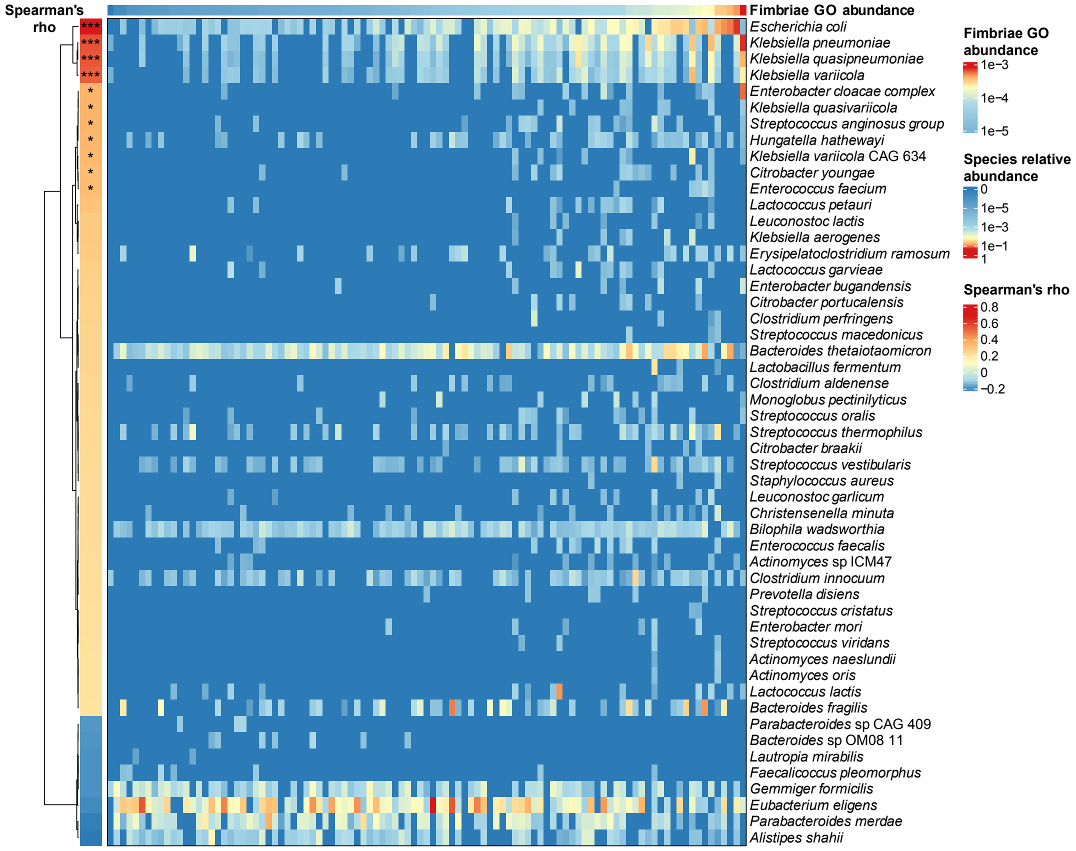
Supplementary Figure 4. Heatmap showing relative abundance of contributing species to gut bacterial motility of the baseline gut microbiome in BNT162b2 vaccinees (N = 101). FDR corrected *P* value of Spearman correlations: ***, *P* < 0.001; **, *P* < 0.01; *, *P* < 0.05.



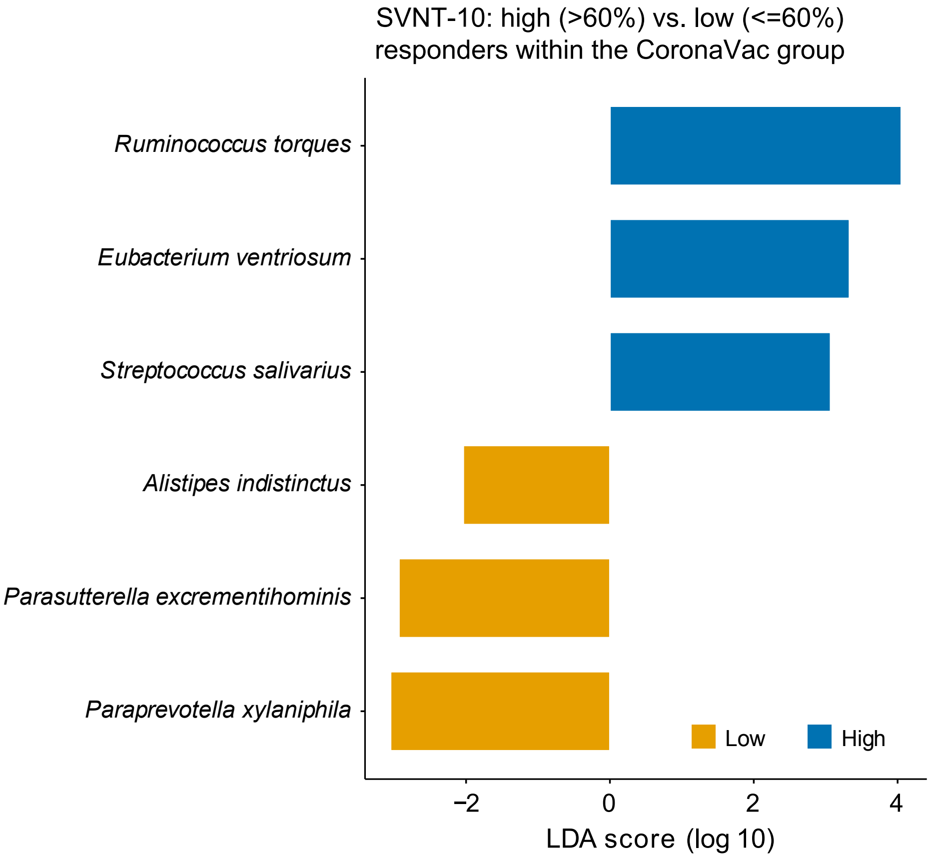
Supplementary Figure 5. Heatmap showing relative abundance of species significantly correlated with bacterial-type flagellum-dependent cell motility (GO:0071973) of the baseline gut microbiome in BNT162b2 vaccinees (n = 101). FDR corrected *P* value of Spearman correlations: ***, *P* < 0.001; **, *P* < 0.01; *, *P* < 0.05.



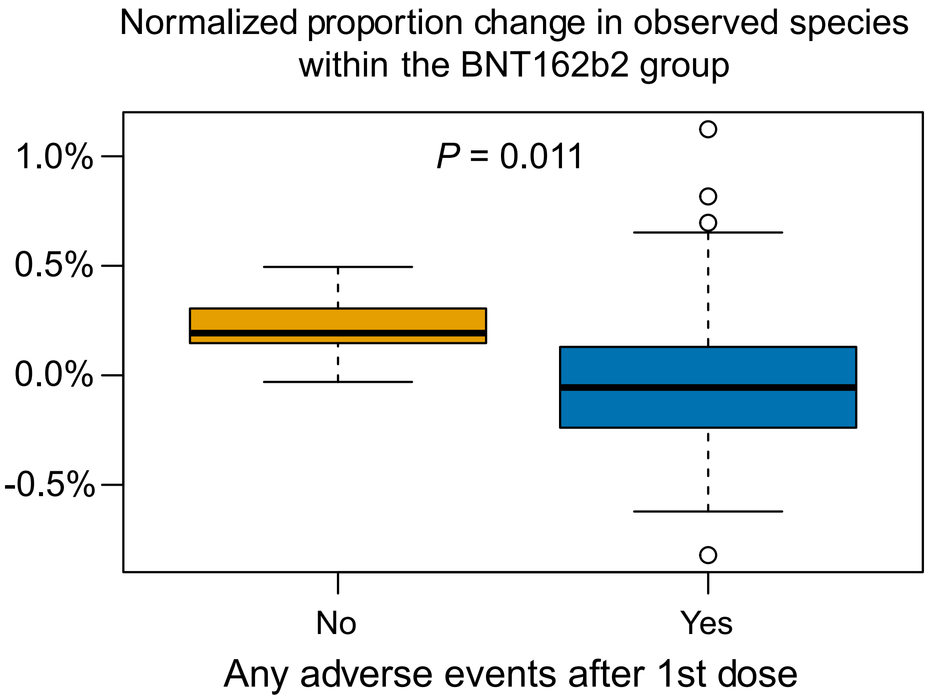
Supplementary Figure 6. Heatmap showing relative abundance of species significantly correlated with bacterial fimbriae (GO:0009289) of the baseline gut microbiome in BNT162b2 vaccinees (n = 101). FDR corrected *P* value of Spearman correlations: ***, *P* < 0.001; **, *P* < 0.01; *, *P* < 0.05.



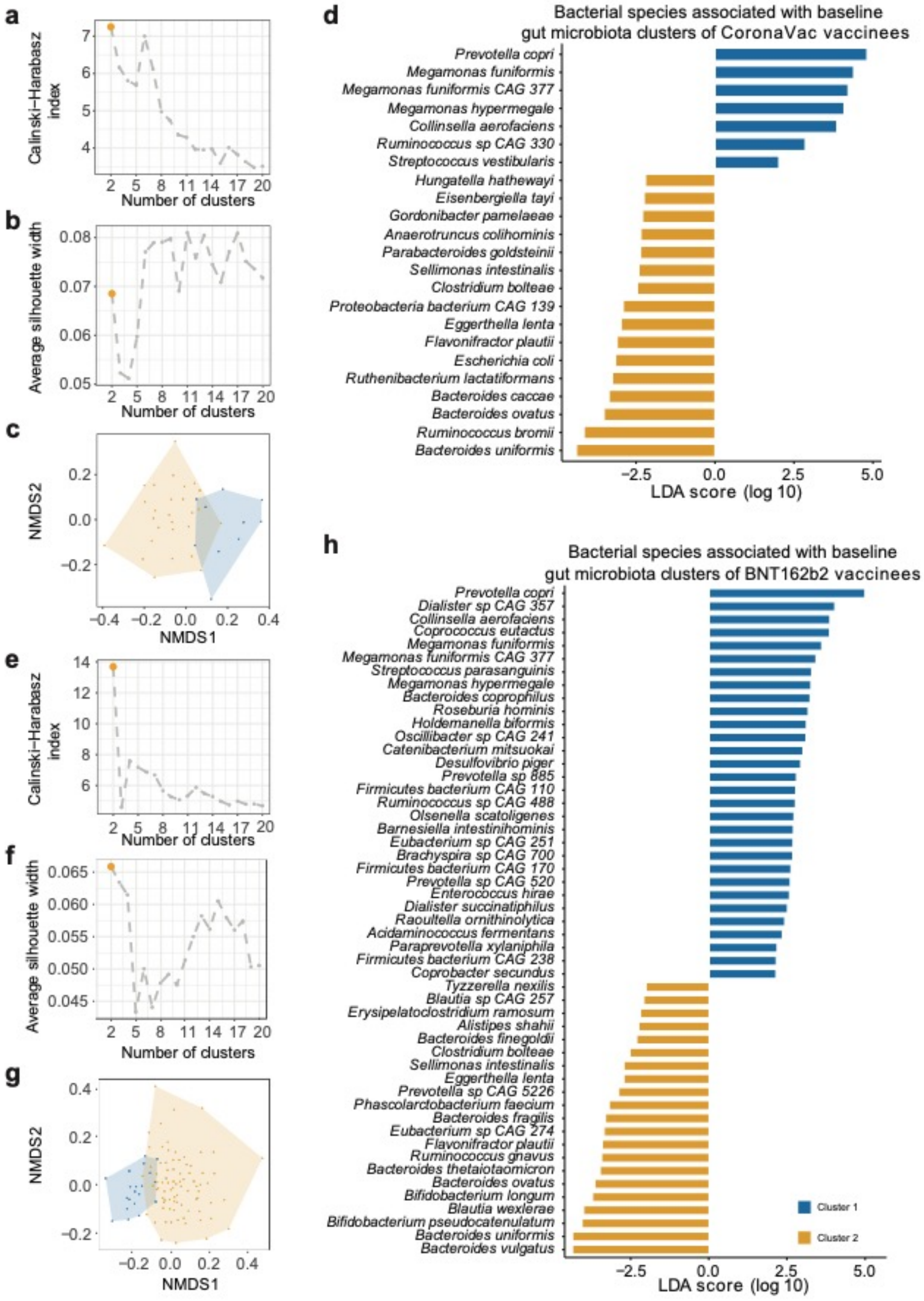
Supplementary Figure 7. Baseline gut bacterial species enriched in high-responders (n = 4) vs. low-responders (n = 11) of CoronaVac vaccine with BMI ≥ 23. Differential gut bacterial species were detected by LEfSe. sVNT-10: sVNT of 10-fold diluted plasma.



Supplementary Figure 8. Normalized proportion change of observed species between the baseline and one month after second dose of BNT162b2 is associated with adverse events after the first dose. Number of participants experienced adverse events after the first vaccine dose: Yes, 90; No, 7.



Supplementary Figure 9. Clustering of baseline gut microbiome samples. a, Calinski-Harabasz index of clustering in CoronaVac vaccinees. **b,** Average sihouette width of clustering in CoronaVac vaccinees (n = 37). **c,** Two clusters of CoronaVac vaccinees (Cluster 1, n = 10; Cluster 2, n = 27). **d,** Bacterial species associated with different gut microbiota clusters of CoronaVac vaccinees. **e,** Calinski-Harabasz index of clustering in BNT162b2 vaccinees (n = 101). **F,** Average silhouette width of clustering in BNT162b2 vaccinees. **g,** Two clusters of CoronaVac vaccinees (Cluster 1, n = 20; Cluster 2, n = 81). **h,** Bacterial species associated with different gut microbiota clusters of BNT162b2 vaccinees. Clustering was based on JSD dissimilarity. Differential gut bacterial species were identified using LEfSe.



Supplementary tables

Supplementary Table 1. Adverse events after first dose and second dose of vaccination

Adverse events	**After 1st dose**			**After 2nd dose**		
	BNT162b2 (N=101)	CoronaVac (N=37)	***p*-value**	BNT162b2 (N=101)	CoronaVac (N=37)	***p*-value**
Injection site pain/burn	84 (84.0)	17 (45.9)	**<0.001**	79 (79.0)	16 (43.2)	**<0.001**
Fatigue	33 (33.0)	3 (8.1)	**0.004**	49 (49.0)	6 (16.2)	**<0.001**
Fever	6 (6.0)	1 (2.7)	0.674	27 (27.0)	0 (0.0)	**<0.001**
Injection site swelling, pruritus, erythema, induration	26 (26.0)	1 (2.7)	**0.001**	28 (28.0)	6 (16.2)	0.186
Myalgia	22 (22.0)	2 (5.4)	**0.023**	26 (26.0)	2 (5.4)	**0.008**
Drowsiness	17 (17.0)	3 (8.1)	0.277	20 (20.0)	2 (5.4)	**0.039**
Headache	11 (11.0)	1 (2.7)	0.180	25 (25.0)	0 (0.0)	**<0.001**
Chills	3 (3.0)	0 (0.0)	0.563	15 (15.0)	1 (2.7)	0.069
Dizziness	6 (6.0)	1 (2.7)	0.674	12 (12.0)	1 (2.7)	0.185
Arthralgia	4 (4.0)	0 (0.0)	0.574	10 (10.0)	0 (0.0)	0.062
Loss of appetite	2 (2.0)	1 (2.7)	1.000	7 (7.0)	0 (0.0)	0.189
Abdominal pain	1 (1.0)	0 (0.0)	1.000	6 (6.0)	0 (0.0)	0.190
Rhinorrhea	1 (1.0)	1 (2.7)	0.469	5 (5.0)	2 (5.4)	1.000
Sore throat	1 (1.0)	0 (0.0)	1.000	6 (6.0)	0 (0.0)	0.190
Diarrhea	2 (2.0)	1 (2.7)	1.000	5 (5.0)	1 (2.7)	1.000
Pruritus	3 (3.0)	2 (5.4)	0.612	4 (4.0)	2 (5.4)	0.661
Coughing	1 (1.0)	0 (0.0)	1.000	4 (4.0)	0 (0.0)	0.574
Constipation	0 (0.0)	0 (0.0)	-	3 (3.0)	0 (0.0)	0.563
Abdominal distension	0 (0.0)	0 (0.0)	-	3 (3.0)	0 (0.0)	0.563
Nausea	1 (1.0)	0 (0.0)	1.000	3 (3.0)	0 (0.0)	0.563
Flushing	1 (1.0)	0 (0.0)	1.000	2 (2.0)	0 (0.0)	1.000
Hypersensitivity	1 (1.0)	0 (0.0)	1.000	1 (1.0)	1 (2.7)	0.469
Muscle spasms	1 (1.0)	0 (0.0)	1.000	1 (1.0)	1 (2.7)	0.469
Nasal Congestion	0 (0.0)	0 (0.0)	-	2 (2.0)	0 (0.0)	1.000
Edema	0 (0.0)	0 (0.0)	-	1 (1.0)	0 (0.0)	1.000
Vomiting	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Tremor	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Eyelid edema	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Nosebleeds	0 (0.0)	0 (0.0)	-	1 (1.0)	0 (0.0)	1.000

Hyposmia	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Ocular congestion	1 (1.0)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	
Others[1]	12 (12.0)	1 (2.70)	0.185	15 (15.0)	1 (2.70)	0.069
Number of adverse events (listed)			**<0.001**			**<0.001**
0	7 (7.0)	14 (37.8)		5 (5.0)	12 (32.4)	
1	39 (39.0)	16 (43.2)		22 (22.0)	15 (40.5)	
2	21 (21.0)	4 (10.8)		19 (19.0)	5 (13.5)	
>=3	33 (33.0)	3 (8.11)		54 (54.0)	5 (13.5)	
Any adverse events	93 (93.0)	23 (62.2)	**<0.001**	95 (95.0)	25 (67.6)	**<0.001**

Data are n (%). Within group valid percentages are shown. There is one missing data in BNT162b2 group. 1. Others include low back pain, increase of appetite, muscle pain, rib pain, eyes pain, palpitations.

Supplementary Table 2. Linear regression model for immunity response between two vaccine groups

	Unadjusted			Adjusted*		
Variables	β	SE	P value	β	SE	P value
AUC of spike RBD IgG						
BNT162b2	Ref	Ref	Ref	Ref	Ref	Ref
CoronaVac	-7088.5	451.3	<0.001	-7098.6	464.3	<0.001
sVNT (inhibition %)						
BNT162b2	Ref	Ref	Ref	Ref	Ref	Ref
CoronaVac	-38.0	2.5	<0.001	-36.2	2.5	<0.001

β, Standardized regression coefficient. sVNT (inhibition %), sVNT level of 10-fold diluted plasma.
*Adjusted for age and comorbidities.

Supplementary Table 3. Immunity response in propensity score matched vaccine groups

Variables	Overall (N=105)	BNT162b2 (N=69)	CoronaVac (N=36)	P Value
AUC of spike RBD IgG	7688.0 (2416.0, 9311.5)	8696.0 (7710.0, 10598.5)	1726.0 (1401.8, 2491.0)	<0.001
sVNT (inhibition %)	93.7 (68.5, 95.8)	95.4 (93.6, 96.4)	57.9 (43.7, 69.4)	<0.001

The data are presented as median (Interquartile range). Matching is based on propensity scores incorporating age and comorbidity.

Supplementary Table 4. Association between participant demographics and immune response

Variables	BNT162b2 (N=101)				CoronaVac (N=37)			
	AUC of spike RBD IgG	P value	sVNT-200	P value	AUC of spikeRBD IgG	P value	sVNT-10	P value
Characteristic								
Age	-0.016	0.872	0.064	0.525	-0.241	0.151	-0.294	0.077
Gender		0.131		0.871		0.768		0.821
Female	9109.0 (7775.0, 11627.0)		42.6 (30.0, 56.2)		1687.5 (1450.5, 2535.0)		55.7 (43.9, 66.9)	
Male	8422.0 (6798.0, 10024.0)		42.9 (35.1, 49.3)		1878.0 (1046.0, 2181.0)		66.5 (38.6, 78.9)	
Body mass index	-0.136	0.176	-0.015	0.880	-0.305	0.066	-0.385	**0.018**
Overweight/Obese		0.074		0.577		0.080		0.069
No	9233.0 (7846.0, 11627.0)		42.7 (31.1, 56.2)		1739.0 (1486.0, 2835.0)		65.3 (42.1, 78.9)	
Yes	8330.0 (7203.0, 9266.0)		41.2 (33.1, 52.2)		1558.0 (1179.5, 1962.5)		49.9 (41.4, 59.3)	
Obese		**0.033**		0.644		0.128		0.140
No	9089.0 (7775.0, 11445.0)		40.9 (33.1, 53.9)		1739.0 (1450.5, 2599.0)		59.0 (43.9, 74.0)	
Yes	7832.5 (6894.0, 8659.0)		44.0 (29.9, 54.5)		1541.0 (979.5, 1727.0)		44.3 (38.6, 47.6)	
Comorbidities								
Hypertension		0.663		0.683		0.608		0.954
No	8701.5 (7675.0, 11048.0)		42.7 (33.3, 53.9)		1627.0 (1353.0, 2459.0)		57.9 (38.6, 67.7)	
Yes	8538.0 (6843.5, 10921.5)		29.9 (23.9, 63.3)		1878.0 (1642.5, 2384)		47.6 (45, 78.6)	
Diabetes mellitus		0.652		0.803		-		-
No	8677.5 (7639.8 , 10958.7)		42.7 (31.6, 54.2)		1725.0 (1450.5, 2416.0)		57.9 (43.2, 69.5)	
Yes	10530.0 (8866.5 , 11263.5)		39.5 (36.4, 52.9)		NA		NA	
Allergy ever		0.262		0.301		0.638		0.768
No	9062.0 (7754.0 , 11627.0)		42.6 (33.2, 56.4)		1627.0 (1450.5, 2416.0)		55.7 (36.5, 69.5)	
Yes	8657.5 (7245.8 , 9999.7)		41.9 (29.3, 51.2)		1753.0 (1353.0, 2611.0)		59.7 (44.3, 65.9)	
Diarrhoea (past 3 month to current)		0.992		0.175		0.558		1.000
No	8616.0 (7699.0 , 10322.7)		40.9 (29.9, 51.7)		1725.0 (1450.5, 2523.0)		53.8 (38.1, 68.5)	
Yes	8785.0 (7124.0 , 11609.3)		43.2 (35.9, 56.1)		1604.0 (1486.0,1878.0)		57.6 (45.6, 66.5)	
Other comorbidities		0.258		0.663		0.676		0.300
No	8777.0 (7651.5, 11251.5)		42.7 (31.6, 54.4)		1725.0 (1450.5, 2523.0)		58.3 (43.2, 69.5)	
Yes	8084.0 (7405.0, 9069.0)		39.4 (33.3, 52.6)		1555.0 (1300.5 , 1809.5)		35.8 (26.9, 44.9)	

Supplementary Table 4. Association between participant demographics and immune response

Variables	BNT162b2 (N=101)				CoronaVac (N=37)			
	AUC of spike RBD IgG	P value	sVNT-200	P value	AUC of spikeRBD IgG	P value	sVNT-10	P value
Current medication								
Antibiotic intake (within 3 month and up to vaccination)		0.477		0.994		-		-
No	8659.0 (7398.0, 10869.5)		42.9 (32.1, 54.1)		1687.5 (1385.5, 2416.0)		55.7 (40.4, 68.5)	
Yes	9331.0 (8162.0, 11058.0)		39.5 (37.9, 56.2)		NA		NA	
Hormonal therapy		0.207		0.503		-		-
No	8696.0 (7675.0, 11058.0)		42.6 (33.3, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	7808.5 (3968.5, 8954.5)		32.8 (11.5, 54.2)		NA		NA	
Immunotherapy		0.226		0.153		-		-
No	8701.5 (7628.0, 11058.0)		42.7 (33.3, 54.5)		1725.0 (1418, 2459)		57.6 (42.1, 69.3)	
Yes	8084.0 (4563.5, 8403.5)		31.1 (15.8, 37.1)		NA		NA	
Probiotics		0.507		0.221		0.532		0.587
No	8683.0 (7398.0, 10679.0)		41.1 (29.9, 54.2)		1753.0 (1450.5, 2523.0)		57.6 (41.4, 74.0)	
Yes	8676.0 (8215.5, 12360.5)		51.2 (37.0, 53.4)		1574.0 (1353.0, 1725.0)		54.4 (42.1, 59.7)	
Vaccination in the past year		0.144		0.222		0.795		0.795
No	8894.5 (7675.0, 11627.0)		43.6 (33.3, 53.9)		1687.5 (1418.0, 2459.0)		55.7 (38.6, 69.3)	
Yes	8297.0 (7230.0, 9511.0)		39.3 (29.9, 54.5)		1727.0 (1385.5, 2480.0)		64.7 (57.7, 72.9)	
Dietary habit								
Vegetarian		-		-		-		-
No	8659.0 (7516.5, 10869.5)		42.6 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Dietary change during vaccination		-		-		-		-
No	8696.0 (7651.5, 10869.5)		42.6 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Alcohol intake (within 2 weeks of vaccination)		0.213		0.266		0.066		0.481
No	8556.5 (7344.5, 10679.0)		41.1 (32.1, 53.5)		1650.0 (1333.0, 2277.0)		51.8 (40.4, 68.7)	

Supplementary Table 4. Association between participant demographics and immune response

Variables	BNT162b2 (N=101)				CoronaVac (N=37)			
	AUC of spike RBD IgG	P value	sVNT-200	P value	AUC of spikeRBD IgG	P value	sVNT-10	P value
Yes	9357.0 (8067.0, 11899.0)		44.9 (35.7, 56.2)		2471.5 (1568.0, 4274.0)		61.8 (53.8, 69.3)	
Exercise								
Regular exercise (Strenuous / moderate)		0.942		0.197		0.404		0.422
No	8723.0 (7344.5, 10626.5)		41.0 (29.3, 51.6)		1313.0 (979.5, 2879.0)		49.9 (24.9, 69.3)	
Yes	8677.5 (7675.0, 11445.0)		43.2 (33.3, 54.5)		1740.0 (1542.5, 2277.0)		57.9 (46.6, 68.7)	
Any adverse events after vaccination								
After first dose		0.995		0.112		0.243		0.298
No	9062.0 (7810.5, 10699.5)		39.0 (24.1, 41.7)		1895.5 (1541, 2587.0)		65.3 (50.6, 67.7)	
Yes	8659.0 (7405.0, 11048.0)		43.1 (33.3, 54.5)		1604.0 (1150, 2175.0)		51.8 (36.9, 69.5)	
After second dose		0.121		0.887		0.737		0.835
No	9701.0 (9062.0, 12659.0)		44.1 (39.3, 46.4)		1634.0 (1385.5, 2325.5)		52.2 (48.7, 72.7)	
Yes	8656.0 (7398.0, 10869.5)		42.6 (33.2, 54.4)		1725.0 (1486, 2459)		58.3 (38.6, 69.3)	

sVNT-10: sVNT level of 10-fold diluted plasma; sVNT-200: sVNT level of 200-fold diluted plasma. Data are correlation coefficient or median (IQR). NA, Not applicable.

Supplementary Table 5. Factors influencing the baseline gut microbiome of the participants

Variables	**Df**	**SumsOfSqs**	**MeanSqs**	**F.Model**	**R^2**	***P* value**
Vaccine groups	1	0.17335307	0.17335307	0.862931074	0.006305075	0.694
Gender	1	0.208147283	0.208147283	1.037007829	0.007622983	0.361
OWOB	1	0.231733764	0.231733764	1.154453596	0.008479	0.219
Obese	1	0.23754336	0.23754336	1.183649662	0.00869157	0.201
Active Hypertension currently	1	0.204290565	0.204290565	1.018087121	0.007430312	0.4
DM currently	1	0.176532299	0.176532299	0.878859166	0.006420708	0.66
Allergy ever	1	0.22353908	0.22353908	1.114798878	0.008130405	0.292
Diarrhea (in the past 3 month and at the moment)	1	0.322621815	0.322621815	1.614701367	0.011906536	0.017
Any other comorbidities	1	0.281072633	0.281072633	1.404684645	0.010222975	0.036
Antibiotic intake past 3 month and/or currently	1	0.284561175	0.284561175	1.422301262	0.010349858	0.046
Hormone intake currently	1	0.220665006	0.220665006	1.100349782	0.008025871	0.269
Immune drug intake currently	1	0.175480944	0.175480944	0.873591419	0.006382469	0.668
Probiotic intake currently	1	0.225624018	0.225624018	1.125538182	0.008268384	0.252
Vaccination in the past year	1	0.113797724	0.113797724	0.564462045	0.004163791	0.998
Dietary habit	1	0.156880744	0.156880744	0.77939718	0.005740173	0.878
Alcohol intake (within 2 weeks prior to first vaccine dose)	1	0.238828656	0.238828656	1.191716793	0.008686507	0.172
Regular exercise (strenuous /moderate)	1	0.318259492	0.318259492	1.592705609	0.011575509	0.017
sVNT-200 Q1 (within BNT162b2 vaccinees)	1	0.2329584	0.2329584	1.143064175	0.011414312	0.246
sVNT-10 >60% (within CoronaVac vaccinees)	1	0.254442111	0.254442111	1.337742476	0.036814133	0.091
AE after the first dose	1	0.421510761	0.421510761	2.121512258	0.015471768	0.002
AE after the second dose	1	0.201213828	0.201213828	1.004482396	0.007385657	0.46
No. of AE after the first dose	3	0.731689735	0.243896578	1.223522584	0.026857046	0.062
No. of AE after the second dose	3	0.564293266	0.188097755	0.937683781	0.020712673	0.667
Age	1	0.238760764	0.238760764	1.191375055	0.008684038	0.177
BMI	1	0.280693939	0.280693939	1.400894948	0.010270423	0.044
Bacterial motility	1	0.810878559	0.810878559	4.132897679	0.029492701	0.001
Baseline observed species	1	0.838276756	0.838276756	4.276932721	0.030489209	0.001
Baseline Simpson diversity	1	1.067447021	1.067447021	5.493400295	0.038824428	0.001
Baseline Shannon diversity	1	0.935264127	0.935264127	4.789192895	0.034016765	0.001

AE, adverse effect(s). *P* values were given by PERMANOVA. sVNT-10: sVNT of 10-fold diluted plasma; sVNT-200: sVNT of 200-fold diluted plasma.

Supplementary Table 6. Difference of dietary habits at baseline and one-month after second dose of vaccination (n=72)

Dietary intake (consumed in the past week)		**Baseline**	**One-month after 2nd dose of vaccination**	***p* value**
1	Pasta, pasta salad, or noodles	70	70	1.00
2	Bread	69	69	1.00
3	Sweet baked foods	66	66	1.00
4	Meats	71	71	1.00
5	Seafood	66	66	1.00
6	Vegetables	72	72	N/A
7	Fruits and products	72	72	N/A
8	Milk and dairy products	58	61	0.25
9	Soup	70	70	1.00
10	Tea and coffee	63	62	1.00
11	Sugars and syrups	56	56	1.00
12	Alcoholic drinks	15	18	0.25
13	Vitamin pills	22	21	1.00

Supplementary Table 7. Mixed effect models for persistently differentially abundant species between low responders and responders

	Baseline abundance		One-month abundance		Model 1		Model 2	
Biomarker	**Low-responders**	**High-responders**	**Low-responders**	**High-responders**	**Effect size**	***P* value**	**Effect size**	***P* value**
CoronaVac								
Bifidobacterium adolescentis	0e+00 (0e+00, 7.03e-03)	9.65e-03 (4.03e-02, 8.46e-02)	0e+00 (0e+00, 1.96e-03)	2.43e-03 (8.06e-03, 3.7e-02)	0.109 (0.027, 0.192)	0.011	0.109 (0.016, 0.203)	0.023
Adlercreutzia equolifaciens	6.29e-05 (5.7e-04, 3.15e-03)	3.17e-03 (3.64e-03, 6.21e-03)	0e+00 (8.52e-05, 7.12e-04)	4.17e-04 (6.08e-04, 2.18e-03)	0.02 (-0.004, 0.044)	0.096	0.019 (-0.007, 0.046)	0.148
Asaccharobacter celatus	0e+00 (1.27e-04, 8.02e-04)	8.7e-04 (1.25e-03, 2.29e-03)	0e+00 (0e+00, 2.59e-04)	7.01e-05 (2.57e-04, 5.72e-04)	0.011 (-0.002, 0.024)	0.083	0.011 (-0.003, 0.025)	0.127
Ruminococcus sp CAG 330	0e+00 (0e+00, 0e+00)	0e+00 (0e+00, 0e+00)	0e+00 (0e+00, 0e+00)	0e+00 (0e+00, 0e+00)	0.011 (0, 0.022)	0.048	0.007 (-0.005, 0.019)	0.257
Mitsuokella multacida	0e+00 (0e+00, 0e+00)	0e+00 (0e+00, 0e+00)	0e+00 (0e+00, 0e+00)	0e+00 (0e+00, 0e+00)	0.01 (0.001, 0.018)	0.025	0.004 (-0.005, 0.012)	0.384
Bacteroides vulgatus	1.5e-02 (5.4e-02, 7.37e-02)	4.31e-03 (9.7e-03, 4.11e-02)	3.81e-02 (6.23e-02, 1.59e-01)	5.97e-03 (2.82e-02, 4.05e-02)	-0.089 (-0.17, -0.007)	0.034	-0.104 (-0.196, -0.012)	0.027
BNT162b2								
Bacteroides sp OM05 12	0e+00 (0e+00, 0e+00)	0e+00 (0e+00, 1.06e-04)	0e+00 (0e+00, 0e+00)	0e+00 (0e+00, 2.38e-04)	0.016 (0.006, 0.026)	0.002	0.015 (0.005, 0.025)	0.003
Bacteroides thetaiotaomicron	6.15e-04 (2.11e-03, 6.63e-03)	1.96e-03 (6.55e-03, 1.5e-02)	1.18e-03 (4.17e-03, 7.59e-03)	3.6e-03 (6.2e-03, 1.91e-02)	0.044 (0.018, 0.07)	0.001	0.045 (0.02, 0.071)	0.001
Fusobacterium mortiferum	0e+00 (0e+00, 0e+00)	0e+00 (0e+00, 0e+00)	0e+00 (0e+00, 0e+00)	0e+00 (0e+00, 0e+00)	-0.011 (-0.022, 0.001)	0.061	-0.011 (-0.022, 0)	0.061

Model 1 is a crude model; Model 2 adjusted for age and time difference between sample collections.

Supplementary Table 8. Full names of differentially abundant pathways between high/low responders

Abbreviation	Full name
ARGININE-SYN4-PWY	L-ornithine biosynthesis II
BIOTIN-BIOSYNTHESIS-PWY	biotin biosynthesis I
COA-PWY-1	superpathway of coenzyme A biosynthesis III (mammals)
COA-PWY	coenzyme A biosynthesis I (prokaryotic)
DAPLYSINESYN-PWY	L-lysine biosynthesis I
FASYN-ELONG-PWY	fatty acid elongation -- saturated
FASYN-INITIAL-PWY	superpathway of fatty acid biosynthesis initiation (E. coli)
FERMENTATION-PWY	mixed acid fermentation
FUC-RHAMCAT-PWY	superpathway of fucose and rhamnose degradation
FUCCAT-PWY	fucose degradation
GALACTARDEG-PWY	D-galactarate degradation I
GLUCARGALACTSUPER-PWY	superpathway of D-glucarate and D-galactarate degradation
GLUCONEO-PWY	gluconeogenesis I
GLUCOSE1PMETAB-PWY	glucose and glucose-1-phosphate degradation
GLUCUROCAT-PWY	superpathway of β-D-glucuronosides degradation
HISTSYN-PWY	L-histidine biosynthesis
NAD-BIOSYNTHESIS-II	NAD salvage pathway III (to nicotinamide riboside)
NONMEVIPP-PWY	methylerythritol phosphate pathway I
NONOXIPENT-PWY	pentose phosphate pathway (non-oxidative branch) I
P105-PWY	TCA cycle IV (2-oxoglutarate decarboxylase)
P4-PWY	superpathway of L-lysine, L-threonine and L-methionine biosynthesis I
P441-PWY	superpathway of N-acetylneuraminate degradation
PEPTIDOGLYCANSYN-PWY	peptidoglycan biosynthesis I (meso-diaminopimelate containing)
POLYISOPRENSYN-PWY	polyisoprenoid biosynthesis (E. coli)
POLYISOPRENSYN-PWY	polyisoprenoid biosynthesis (E. coli)
PWY-241	C4 photosynthetic carbon assimilation cycle, NADP-ME type

PWY-2942	L-lysine biosynthesis III
PWY-4242	
PWY-5097	L-lysine biosynthesis VI
PWY-5104	L-isoleucine biosynthesis IV
PWY-5304	superpathway of sulfur oxidation (Acidianus ambivalens)
PWY-5345	superpathway of L-methionine biosynthesis (by sulfhydrylation)
PWY-5367	petroselinate biosynthesis
PWY-5384	sucrose degradation IV (sucrose phosphorylase)
PWY-5464	superpathway of cytosolic glycolysis (plants), pyruvate dehydrogenase and TCA cycle
PWY-5675	nitrate reduction V (assimilatory)
PWY-5686	UMP biosynthesis I
PWY-5690	TCA cycle II (plants and fungi)
PWY-5723	Rubisco shunt
PWY-5837	2-carboxy-1,4-naphthoquinol biosynthesis
PWY-5838	superpathway of menaquinol-8 biosynthesis I
PWY-5840	superpathway of menaquinol-7 biosynthesis
PWY-5845	superpathway of menaquinol-9 biosynthesis
PWY-5850	superpathway of menaquinol-6 biosynthesis
PWY-5860	superpathway of demethylmenaquinol-6 biosynthesis I
PWY-5861	superpathway of demethylmenaquinol-8 biosynthesis I
PWY-5862	superpathway of demethylmenaquinol-9 biosynthesis
PWY-5896	superpathway of menaquinol-10 biosynthesis
PWY-5897	superpathway of menaquinol-11 biosynthesis
PWY-5898	superpathway of menaquinol-12 biosynthesis
PWY-5899	superpathway of menaquinol-13 biosynthesis
PWY-5913	partial TCA cycle (obligate autotrophs)
PWY-5971	palmitate biosynthesis (type II fatty acid synthase)
PWY-5989	stearate biosynthesis II (bacteria and plants)
PWY-6168	flavin biosynthesis III (fungi)

PWY-622	starch biosynthesis
PWY-6282	palmitoleate biosynthesis I (from (5Z)-dodec-5-enoate)
PWY-6284	superpathway of unsaturated fatty acids biosynthesis (E. coli)
PWY-6285	superpathway of fatty acids biosynthesis (E. coli)
PWY-6385	peptidoglycan biosynthesis III (mycobacteria)
PWY-6386	UDP-N-acetylmuramoyl-pentapeptide biosynthesis II (lysine-containing)
PWY-6387	UDP-N-acetylmuramoyl-pentapeptide biosynthesis I (meso-diaminopimelate containing)
PWY-6519	8-amino-7-oxononanoate biosynthesis I
PWY-6545	pyrimidine deoxyribonucleotides de novo biosynthesis III
PWY-6608	guanosine nucleotides degradation III
PWY-6700	queuosine biosynthesis I (de novo)
PWY-6737	starch degradation V
PWY-6749	CMP-legionaminate biosynthesis I
PWY-6969	TCA cycle V (2-oxoglutarate synthase)
PWY-7003	glycerol degradation to butanol
PWY-7115	C4 photosynthetic carbon assimilation cycle, NAD-ME type
PWY-7117	C4 photosynthetic carbon assimilation cycle, PEPCK type
PWY-7184	pyrimidine deoxyribonucleotides de novo biosynthesis I
PWY-7198	pyrimidine deoxyribonucleotides de novo biosynthesis IV
PWY-7200	superpathway of pyrimidine deoxyribonucleoside salvage
PWY-7209	superpathway of pyrimidine ribonucleosides degradation
PWY-7210	pyrimidine deoxyribonucleotides biosynthesis from CTP
PWY-7211	superpathway of pyrimidine deoxyribonucleotides de novo biosynthesis
PWY-7219	adenosine ribonucleotides de novo biosynthesis
PWY-7221	guanosine ribonucleotides de novo biosynthesis
PWY-7234	inosine-5 p-phosphate biosynthesis III
PWY-724	superpathway of L-lysine, L-threonine and L-methionine biosynthesis II
PWY-7242	D-fructuronate degradation
PWY-7315	dTDP-N-acetylthomosamine biosynthesis

PWY-7388	octanoyl-[acyl-carrier protein] biosynthesis (mitochondria, yeast)
PWY-7664	oleate biosynthesis IV (anaerobic)
PWY0-166	superpathway of pyrimidine deoxyribonucleotides de novo biosynthesis (E. coli)
PWY0-781	aspartate superpathway
PWY0-862	(5Z)-dodecenoate biosynthesis I
PWY4LZ-257	superpathway of fermentation (Chlamydomonas reinhardtii)
PWY4LZ-257	superpathway of fermentation (Chlamydomonas reinhardtii)
PWY66-399	gluconeogenesis III
RIBOSYN2-PWY	flavin biosynthesis I (bacteria and plants)
SO4ASSIM-PWY	assimilatory sulfate reduction I
SULFATE-CYS-PWY	superpathway of sulfate assimilation and cysteine biosynthesis
THISYNARA-PWY	superpathway of thiamine diphosphate biosynthesis III (eukaryotes)
TRPSYN-PWY	L-tryptophan biosynthesis
UDPNAGSYN-PWY	UDP-N-acetyl-D-glucosamine biosynthesis I

Supplementary Table 9. Logistic regression models for having adverse effect after first dose of vaccinatione based on baseline gut microbiota clusters

		Model 1				Model 2			
Vaccine group	**Dose**	**OR**	**2.50%**	**97.50%**	**p**	**OR**	**2.50%**	**97.50%**	**p**
BNT162b2 (Cluster 2 vs. Cluster 1)	1	6.93	1.41	34.19	**0.017**	13.78	2.48	76.6	**0.003**
	2	7.41	1.14	47.96	**0.036**	9.55	1.35	67.43	**0.024**
CoronaVac (Cluster 2 vs. Cluster 1)	1	6.67	1.34	33.12	**0.02**				
	2	1.58	0.35	7.17	0.551				

Model 1 is a crude model; Model 2 adjusted for alcohol drinking within 2 weeks prior to the 1st dose of vaccination, which was significantly associated with cluster membership in BNT162b2 vaccinees.

Supplementary Table 10. The association between immunity response and adverse events after first dose of vaccination (Overall)

Adverse events	**BNT162b2 (N=101)**				**CoronaVac (N=37)**			
	AUC of spikeRBD IgG	P value	sVNT-200	P value	AUC of spikeRBD IgG	P value	sVNT-10	P value
Any adverse events after first dose		0.995		0.112		0.244		0.298
No	9062.0 (7810.5, 10699.5)		39.0 (24.1, 41.7)		1895.5 (1541.0, 2587.0)		65.3 (50.6, 67.7)	
Yes	8659.0 (7405.0, 11048.0)		43.1 (33.3, 54.5)		1604.0 (1150.0, 2175.0)		51.8 (36.9, 69.5)	
Injection site pain/burn		0.898		0.206		0.424		0.478
No	8497.5 (7459.0, 11880.0)		39.2 (34.5, 45.3)		1726.0 (1542.5, 2523.0)		62.2 (46.6, 67.1)	
Yes	8677.5 (7516.5, 10679.0)		43.2 (32.2, 55.4)		1604.0 (1046.0, 2373.0)		51.8 (24.9, 69.6)	
Fatigue		0.593		**0.032**		0.244		**0.052**
No	8656.0 (7398.0, 10869.5)		39.4 (29.9, 52.6)		1740.0 (1418.0, 2587.0)		59.0 (44.3, 69.6)	
Yes	8723.0 (7732.0, 11058.0)		44.9 (40.1, 56.5)		1544.0 (1295.0, 1551.0)		35.2 (26.5, 40.4)	
Fever		0.499		**0.046**		-		-
No	8657.5 (7405.0, 11058.0)		41.2 (33.1, 52.6)		1726.0 (1450.5, 2523.0)		57.9 (43.2, 69.5)	
Yes	10408.5 (8347.0, 10667.0)		58.1 (51.4, 60.9)		NA		NA	
Injection site swelling, pruritus, erythema, induration		0.398		0.162		0.758		0.486
No	9065.5 (7628.0, 11627.0)		40.9 (31.1, 52.6)		1687.5 (1385.5, 2523.0)		55.7 (40.4, 68.5)	
Yes	8301.5 (7229.0, 10287.0)		48.4 (36.1, 56.5)					
Myalgia		0.163		0.825		**0.036**		0.090
No	9065.5 (7732.0, 11627.0)		42.0 (33.3, 54.4)		1727.0 (1484.5, 2523)		58.3 (45, 69.5)	
Yes	8384.5 (7229.0, 9266.0)		47.4 (28.7, 54.5)		1036.9 (819.7, 1254)		29.6 (17.1, 42.1)	
Drowsiness		0.233		0.121		0.292		0.267
No	8538.0 (7398.0, 10869.5)		41.2 (32.1, 52.6)		1627.0 (1353, 2459)		52.8 (38.6, 69.3)	
Yes	9402.0 (8347.0, 12084)		52.0 (40.8, 55.5)		1753.0 (1739, 3614.5)		64.7 (62.2, 74.6)	
Headache		0.092		0.783		-		-
No	8847.0 (7732.0, 11058.0)		42.9 (33.1, 54.4)		1726.0 (1385.5, 2523.0)		57.9 (40.4, 69.5)	
Yes	7675.0 (6676.0, 8535.0)		41.3 (38.3, 50.2)		NA		NA	
Chills		0.793		0.163		-		-
No	8696.0 (7628.0, 11048.0)		42.6 (33.1, 53.9)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	8347 .0 (7620.5, 9702.5)		57.8 (48.9, 61.5)		NA		NA	

Supplementary Table 10. The association between immunity response and adverse events after first dose of vaccination (Overall)

Adverse events	**BNT162b2 (N=101)**				**CoronaVac (N=37)**			
	AUC of spikeRBD IgG	P value	sVNT-200	P value	AUC of spikeRBD IgG	P value	sVNT-10	P value
Dizziness		0.429		0.372		-		-
No	8701.5 (7628.0, 11445.0)		42.0 (33.3, 52.6)		1687.5 (1385.5, 2416.0)		55.7 (40.4, 68.5)	
Yes	8301.5 (7229.0, 9476.0)		56.5 (28.4, 57.8)		NA		NA	
Arthralgia		0.100		0.937		-		-
No	8709.5 (7658.0, 11251.5)		42.7 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	7452.0 (6379.5, 8191.0)		41.6 (33.9, 50.2)		NA		NA	
Loss of appetite		0.951		0.284		-		-
No	8677.5 (7405.0, 11058.0)		42.0 (33.1, 54.4)		1726.0 (1450.5, 2523.0)		57.9 (43.2, 69.5)	
Yes	8597.0 (8347.0, 8847.0)		51.3 (44.9, 57.8)		NA		NA	
Abdominal pain		0.253		0.556		-		-
No	8659.0 (7516.5, 10869.5)		42.6 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes					NA		NA	
Rhinorrhea		0.146		0.268		-		-
No	8696.0 (7651.5, 11053.0)		42.9 (33.3, 54.4)		1726.0 (1450.5, 2523.0)		57.9 (43.2, 69.5)	
Yes					NA		NA	
Sore throat		0.234		0.917		-		-
No	8659.0 (7516.5, 10869.5)		42.9 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes					NA		NA	
Diarrhea		0.530		0.331		-		-
No	8677.5 (7628.0, 11058.0)		42.0 (33.1, 54.4)		1726.0 (1450.5, 2523.0)		57.9 (43.2, 69.5)	
Yes	8038.0 (7229.0, 8847.0)		50.7 (44.9, 56.5)		NA		NA	
Pruritus		0.856		0.746		0.330		0.126
No	8659.0 (7628.0, 11048.0)		42.6 (33.1, 54.4)		1650.0 (1385.5, 2416.0)		53.8 (40.4, 67.1)	
Yes	8723.0 (7504.0, 10175.0)		43.2 (39.6, 50.0)		2294.0 (1977.0, 2611.0)		75.3 (69.6, 81.0)	
Coughing		-		-		-		-
No	8696.0 (7651.5, 11053.0)		42.6 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Constipation		-		-		-		-
No	8677.5 (7516.5, 11053.0)		42.7 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	

Supplementary Table 10. The association between immunity response and adverse events after first dose of vaccination (Overall)

Adverse events	**BNT162b2 (N=101)**				**CoronaVac (N=37)**			
	AUC of spikeRBD IgG	P value	sVNT-200	P value	AUC of spikeRBD IgG	P value	sVNT-10	P value
Abdominal distension		-		-		-		-
No	8677.5 (7516.5, 11053.0)		42.7 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Nausea		-		-		-		-
No	8696.0 (7651.5, 11053.0)		42.6 (33.2, 54.1)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Flushing		-		-		-		-
No	8696.0 (7516.5, 11053.0)		42.6 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Hypersensitivity		-		-		-		-
No	8696.0 (7516.5, 11053.0)		42.9 (33.3, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Muscle spasms		-		-		-		-
No	8696.0 (7516.5, 11053.0)		42.9 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Nasal Congestion		-		-		-		--
No	8696.0 (7516.5, 11053.0)		42.9 (33.3, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Edema		-		-		-		-
No	8696.0 (7516.5, 11053.0)		42.9 (33.3, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Vomiting		-		-		-		-
No	8696.0 (7516.5, 11053.0)		42.9 (33.3, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Tremor		-		-		-		-
No	8696.0 (7516.5, 11053.0)		42.9 (33.3, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Eyelid edema				-				-
No	8696.0 (7516.5, 11053.0)		42.9 (33.3, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	

Supplementary Table 10. The association between immunity response and adverse events after first dose of vaccination (Overall)

Adverse events	BNT162b2 (N=101)				CoronaVac (N=37)			
	AUC of spikeRBD IgG	P value	sVNT-200	P value	AUC of spikeRBD IgG	P value	sVNT-10	P value
Nosebleeds		-		-		-		-
No	8696.0 (7516.5, 11053.0)		42.9 (33.3, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Hyposmia		-		-		-		-
No	8696.0 (7516.5, 11053.0)		42.9 (33.3, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Ocular congestion		-		-		-		-
No	8696.0 (7516.5, 11053.0)		42.9 (33.3, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Number of adverse events (listed)		0.933		0.018		0.139		0.204
0	9062.0 (7810.5, 10699.5)		39.0 (24.1, 41.7)		1895.5 (1541.0, 2587.0)		65.3 (50.6, 67.7)	
1	8659.0 (7398.0, 11356.0)		39.4 (30.5, 53.5)		1739.0 (1399.5, 2492.0)		57.9 (39.7, 73.8)	
2	8238.0 (7298.0, 9476.0)		43.1 (29.9, 50.0)		1150.0 (1012.8, 1406.0)		40.4 (28.2, 43.9)	
>=3	8707.0 (7994.0, 11058.0)		51.0 (40.1, 56.5)		1977.0 (1398.4, 3726.5)		69.6 (43.4, 77.1)	
Others[1]		0.429		0.337		-		-
No	8715.0 (7651.5, 11251.5)		42.0 (32.1, 54.1)		1687.5 (1385.5, 2523.0)		57.9 (40.4, 69.5)	
Yes	8301.5 (6861.0, 9497.5)		47.4 (37.8, 57.1)		NA		NA	

sVNT-10: sVNT of 10-fold diluted plasma; sVNT-200: sVNT of 200-fold diluted plasma. Data are median (IQR). NA, Not applicable. There is one missing data in BNT162b2 group. 1. Others include low back pain, increase of appetite, muscle pain, rib pain, eyes pain, palpitations.

Supplementary Table 11. The association between immunity response and adverse events after second dose of vaccination (Overall)

Adverse events	**BNT162b2 (N=101)**				**CoronaVac (N=37)**			
	AUC of spikeRBD IgG	p-value	sVNT-200	p-value	AUC of spikeRBD IgG	p-value	sVNT-10	p-value
Any adverse events after second dose		0.121		0.887		0.737		0.835
No	9701.0 (9062.0, 12659.0)		44.1 (39.3, 46.4)		1634.0 (1385.5, 2325.5)		52.2 (48.7, 72.7)	
Yes	8656.0 (7398.0, 10869.5)		42.6 (33.2, 54.4)		1725.0 (1486.0, 2459.0)		58.3 (38.6, 69.3)	
Injection site pain/burn		0.986		0.213		0.867		0.797
No	8576.0 (7732.0, 11664.0)		37.0 (33.1, 51.4)		1725.0 (1483.0, 2181.0)		53.8 (45.7, 66.5)	
Yes	8696.0 (7516.5, 10679.0)		43.2 (33.3, 55.4)		1776.0 (1150.0, 2857.0)		57.9 (31.3, 69.5)	
Fatigue		0.352		0.098		0.363		0.533
No	8659.0 (7398.0, 9973.0)		40.1 (29.9, 52.6)		1753.0 (1385.5, 2599.0)		58.3 (43.2, 69.5)	
Yes	8707.0 (7732.0, 11698.0)		43.9 (37, 55.5)		1551.0 (1486.0, 1650.0)		51.6 (35.2, 66.1)	
Fever		0.347		0.119		-		-
No	8538.0 (7391.0, 10691.0)		41.2 (29.9, 52.6)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	9402.0 (7998.0, 11251.5)		48.3 (36.1, 56.7)		NA		NA	
Injection site swelling, pruritus, erythema, induration		0.844		0.078		0.342		0.857
No	8715.0 (7516.5, 10869.5)		41.1 (30.5, 52.4)		1604.0 (1385.5, 2416.0)		53.8 (40.4, 73.8)	
Yes	8479.5 (7284.5, 11251.5)		48.4 (36.2, 57.4)		1927.5 (1650.0, 2835.0)		66.0 (44.3, 67.7)	
Myalgia		0.623		0.517		0.817		0.769
No	8785.0 (7628.0, 11627.0)		43.1 (33.3, 55.2)		1727.0 (1385.5, 2523.0)		57.6 (40.4, 69.5)	
Yes	8556.5 (7405.0, 9904.0)		40.3 (28.7, 52.5)		1641.5 (1558.0, 1725.0)		52.7 (45.7, 59.7)	
Drowsiness		0.676		0.250		0.108		**0.048**
No	8616.0 (7540.0, 10869.5)		41.2 (30.5, 53.5)		1650.0 (1385.5, 2416.0)		53.8 (40.4, 67.1)	
Yes	8777.0 (7261.0, 11764.5)		46.6 (40.0, 55.4)		3828.5 (2181.0, 5476.0)		81.9 (79.3, 84.6)	
Headache		0.702		0.937		-		-
No	8707.0 (7710.0, 11159.0)		43.1 (33.2, 53.5)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	8422.0 (7298.0, 11048.0)		41.3 (36.3, 54.4)		NA		NA	
Chills		0.025		0.311		-		-

Supplementary Table 11. The association between immunity response and adverse events after second dose of vaccination (Overall)

Adverse events	BNT162b2 (N=101)				CoronaVac (N=37)			
	AUC of spikeRBD IgG	p-value	sVNT-200	p-value	AUC of spikeRBD IgG	p-value	sVNT-10	p-value
No	8537.0 (7298.0, 10586.0)		41.3 (33.1, 52.6)		1687.5 (1385.5, 2523.0)		55.7 (40.4, 68.5)	
Yes	10245.0 (8884.0, 11812.0)		50.0 (36.7, 56.2)		NA		NA	
Dizziness		0.820		0.311		-		-
No	8657.5 (7540.0, 10874.5)		42.0 (32.1, 52.6)		1687.5 (1385.5, 2416.0)		55.7 (40.4, 68.5)	
Yes	9091.5 (7428.5, 11337.5)		49.0 (36.3, 57.3)		NA		NA	
Arthralgia		0.850		0.690		-		-
No	8677.5 (7628.0, 11058.0)		42.7 (33.3, 54.5)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	8681.5 (7405.0, 9904.0)		42.2 (28.4, 52.5)		NA		NA	
Loss of appetite		0.317		0.317		-		-
No	8659.0 (7391.0, 11048.0)		41.3 (33.1, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	8847.0 (8501.5, 10674.5)		52.2 (42.7, 53.9)		NA		NA	
Abdominal pain		0.744		0.994		-		-
No	8677.5 (7628.0, 11048.0)		42.7 (33.1, 54.5)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	8949.0 (6519.0, 11445.0)		44.5 (35.7, 52.2)		NA		NA	
Rhinorrhea		0.601		0.236		0.243		0.300
No	8659.0 (7516.5, 11053.0)		41.3 (33.2, 53.5)		1727.0 (1450.5, 2523.0)		58.3 (43.2, 69.5)	
Yes	8256.0 (6519.0, 10287.0)		53.9 (48.3, 56.5)		1268.8 (979.5, 1558.0)		42.1 (38.6, 45.7)	
Sore throat		0.051		0.856		-		-
No	8616.0 (7405.0, 10586.0)		43.0 (33.1, 54.5)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	12040.5 (11445.0, 12087.0)		40.8 (33.3, 53.9)		NA		NA	
Diarrhea		0.507		0.420		-		-
No	8696.0 (7651.5, 10869.5)		43.1 (32.1, 54.5)		1726.0 (1450.5, 2523.0)		57.9 (43.2, 69.5)	
Yes	7846.0 (6519.0, 11445.0)		39.4 (33.3, 40.6)		NA		NA	
Pruritus		0.840		0.718		0.216		0.270
No	8657.5 (7516.5, 11053.0)		42.0 (33.2, 54.4)		1650.0 (1385.5, 2277.0)		53.8 (40.4, 68.5)	
Yes	8709.5 (7113.0, 10175.0)		47.6 (35.8, 54.4)		2535.0 (2459.0, 2611.0)		72.9 (64.7, 81.0)	
Coughing		0.329		0.196		-		-

Supplementary Table 11. The association between immunity response and adverse events after second dose of vaccination (Overall)

Adverse events	**BNT162b2 (N=101)**				**CoronaVac (N=37)**			
	AUC of spikeRBD IgG	p-value	sVNT-200	p-value	AUC of spikeRBD IgG	p-value	sVNT-10	p-value
No	8657.5 (7516.5, 10869.5)		42.0 (32.1, 54.1)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	10672.5 (8403.0, 12651.5)		51.9 (44.2, 58.2)		NA		NA	
Constipation		**0.031**		0.182		-		-
No	8707.0 (7688.0, 11058.0)		42.9 (33.3, 54.5)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	6519.0 (6024.5, 6962.0)		28.4 (17.0, 38.4)		NA		NA	
Abdominal distension		0.396		0.443		-		-
No	8696.0 (7628.0, 11058.0)		42.6 (33.1, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	8347.0 (7433.0, 8527.0)		48.3 (43.9, 53.1)		NA		NA	
Nausea		**0.031**		0.711		-		-
No	8656.0 (7405.0, 10667.0)		42.9 (33.1, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	12084.0 (11764.5, 12873.5)		41.0 (40.8, 48.1)		NA		NA	
Flushing		0.740		0.452		-		-
No	8677.5 (7405.0, 11058.0)		42.7 (33.3, 54.5)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	8358.5 (7994.0, 8723.0)		34.8 (26.4, 43.2)		NA		NA	
Hypersensitivity		-		-		-		-
No	8696.0 (7516.5, 11053.0)		42.9 (33.3, 54.4)		1687.5 (1385.5, 2523.0)		55.7 (40.4, 68.5)	
Yes	NA		NA		NA		NA	
Muscle spasms		-		-		-		-
No	8659.0 (7516.5, 11053.0)		42.9 (33.2, 54.4)		1687.5 (1385.5, 2523.0)		55.7 (40.4, 68.5)	
Yes	NA		NA		NA		NA	
Nasal Congestion		0.667		0.853		-		-
No	8677.5 (7628.0, 11048.0)		42.7 (33.1, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	8257.5 (4888.0, 11627.0)		45.0 (33.3, 56.8)		NA		NA	
Edema		-		-		-		-
No	8659.0 (7516.5, 11053.0)		42.9 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Vomiting		-		-		-		-

Supplementary Table 11. The association between immunity response and adverse events after second dose of vaccination (Overall)

Adverse events	**BNT162b2 (N=101)**				**CoronaVac (N=37)**			
	AUC of spikeRBD IgG	p-value	sVNT-200	p-value	AUC of spikeRBD IgG	p-value	sVNT-10	p-value
No	8659.0 (7516.5, 11053.0)		42.7 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Tremor		-		-		-		-
No	8659.0 (7516.5, 11053.0)		42.7 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Eyelid edema		-		-		-		-
No	8659.0 (7516.5, 11053.0)		42.7 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Nosebleeds		-		-		-		-
No	8659.0 (7516.5, 11053.0)		42.7 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Hyposmia		-		-		-		-
No	8659.0 (7516.5, 11053.0)		42.7 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Ocular congestion		-		-		-		-
No	8659.0 (7516.5, 11053.0)		42.7 (33.2, 54.4)		1725.0 (1418.0, 2459.0)		57.6 (42.1, 69.3)	
Yes	NA		NA		NA		NA	
Number of adverse events (listed)		0.320		0.064		0.531		0.702
0	9701.0 (9062.0, 12659.0)		44.1 (39.3, 46.4)		1634.0 (1385.5, 2325.5)		52.2 (48.7, 72.7)	
1	8007.0 (6875.0, 9575.0)		41.9 (29.9, 52.6)		1725.0 (1399.0, 2416.0)		51.8 (36.5, 67.0)	
2	8576.0 (6589.5, 10089.5)		35.9 (26.2, 45.8)		1650.0 (1486.0, 2835.0)		65.9 (57.6, 66.1)	
>=3	8715.0 (7846.0, 11445.0)		44.3 (39.4, 56.5)		1977.0 (1558.0, 2181.0)		69.6 (45.7, 79.3)	
Others[1]		0.595		0.300		-		-
No	8707.0 (7675.0, 11058.0)		41.3 (31.1, 54.4)		1687.5 (1385.5, 2523.0)		57.9 (40.4, 69.5)	
Yes	8347.0 (7415.5, 9748.5)		46.4 (37.8, 55.0)		NA		NA	

sVNT-10: sVNT of 10-fold diluted plasma; sVNT-200: sVNT of 200-fold diluted plasma. Data are median (IQR). NA, Not applicable. There is one missing data in BNT162b2 group.

1. Others include low back pain, increase of appetite, muscle pain, rib pain, eyes pain, palpitations.

Supplementary references

1. Perera RA, Mok CK, Tsang OT. *et al*. Serological assays for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), March 2020. *Euro Surveill* 2020;**25**:200042. doi:10.2807/1560-7917.ES.2020.25.16.2000421
2. Perera R, Ko R, Tsang OT. *et al.* Evaluation of a SARS-CoV-2 surrogate virus neutralization test for detection of antibody in human, canine, cat, and hamster sera. *J Clin Microbiol* 2021;**59**:e02504-20. doi:10.1128/JCM.02504-20
3. Zuo T, Zhang F, Liu GCY. *et al*. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. *Gastroenterology* 2020;**159**:944–955. doi:10.1053/j.gastro.2020.05.048
4. Yeoh YK, Zuo T, Liu GCY. *et al*. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut* 2021;**70**:698-706. doi:10.1136/gutjnl-2020-323020
5. Guittar J, Shade A, Litchman E. Trait-based community assembly and succession of the infant gut microbiome. *Nat Commun* 2019;**10**:512. doi:10.1038/s41467-019-08377-w.
6. Zhang X, Yi N. NBZIMM: negative binomial and zero-inflated mixed models, with application to microbiome/metagenomics data analysis. *BMC Bioinformatics* 2020;**21**:488. doi:10.1186/s12859-020-03803-z
7. Segata N, Lzard J, Waldron L, *et al*. Metagenomic biomarker discovery and explanation. *Genome Biol* 2011;**12**: R60. doi: 10.1186/gb-2011-12-6-r60.
8. Pernigoni N, Zagato E, Calcinotto A, *et al*. Commensal bacteria promote endocrine resistance in prostate cancer through androgen biosynthesis. *Science* 2021; **374**: 216-224. doi: 10.1126/science.abf8403.