Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Immunogenicity and reactogenicity of SARS-CoV-2 mRNA and inactivated vaccines in healthy adolescents

Yu-Lung Lau (✉ lauylung@hku.hk)
The University of Hong Kong

Jaime Rosa Duque
Department of Paediatrics and Adolescent Medicine, The University of Hong Kong
https://orcid.org/0000-0002-5292-5510

Xiwei Wang
The University of Hong Kong

Daniel Leung
Department of Paediatrics and Adolescent Medicine, The University of Hong Kong

Samuel Cheng
University of Hong Kong https://orcid.org/0000-0001-7293-2331

Carolyn Cohen
School of Public Health, The University of Hong Kong

Xiaofeng Mu
Department of Paediatrics and Adolescent Medicine, The University of Hong Kong

Asmaa Hachim
School of Public Health, The University of Hong Kong

Yanmei Zhang
Department of Paediatrics and Adolescent Medicine, The University of Hong Kong

Sau-Man Chan
Department of Paediatrics and Adolescent Medicine, The University of Hong Kong

Sara Chaothai
School of Public Health, The University of Hong Kong

Kelvin Kwan
School of Public Health, The University of Hong Kong

Karl Chan
University of Hong Kong

John Li
University of Hong Kong

Leo Luk
University of Hong Kong

Leo Tsang
University of Hong Kong
Wilfred Wong
Department of Paediatrics and Adolescent Medicine, The University of Hong Kong
Cheuk-Hei Cheang
Department of Paediatrics and Adolescent Medicine, The University of Hong Kong
Timothy Hung
Department of Paediatrics and Adolescent Medicine, The University of Hong Kong
https://orcid.org/0000-0002-6195-230X
Jennifer Lam
Department of Paediatrics and Adolescent Medicine, The University of Hong Kong
Gilbert Chua
Department of Paediatrics and Adolescent Medicine, The University of Hong Kong
Winnie Tso
Department of Paediatrics and Adolescent Medicine, The University of Hong Kong
Patrick Ip
Department of Paediatrics and Adolescent Medicine, The University of Hong Kong
Niloufar Kavian
School of Public Health, The University of Hong Kong
Wing Leung
Department of Paediatrics and Adolescent Medicine, The University of Hong Kong
Sophie Valkenburg
The University of Hong Kong https://orcid.org/0000-0002-0768-9926
Malik Peiris
University of Hong Kong https://orcid.org/0000-0001-8217-5995
WENWEI TU
University of Hong Kong https://orcid.org/0000-0002-6801-8798
Masashi Mori

Article

Keywords: COVID-19, vaccine, BNT162b2, CoronaVac, immunity, adolescent

Posted Date: March 8th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1327020/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Version of Record: A version of this preprint was published at Nature Communications on June 28th, 2022. See the published version at https://doi.org/10.1038/s41467-022-31485-z.

Immunogenicity and reactogenicity of SARS-CoV-2 mRNA and inactivated vaccines in healthy adolescents

Jaime S Rosa Duque,[1,*] Xiwei Wang,[1,*] Daniel Leung,[1,*] Samuel MS Cheng,[2*] Carolyn A Cohen,[2,*] Xiaofeng Mu,[1] Asmaa Hachim,[2,3] Yanmei Zhang,[1] Sau-Man Chan,[1] Sara Chaothai,[2] Kelvin KH Kwan,[2] Karl CK Chan,[2] John KC Li,[2] Leo LH Luk,[2] Leo CH Tsang,[2] Wilfred HS Wong,[1] Cheuk-Hei Cheang,[1] Timothy K Hung,[1] Jennifer HY Lam,[1] Gilbert T Chua,[1] Winnie WY Tso,[1,4] Patrick Ip,[1] Masashi Mori,[5] Niloufar Kavian,[2,6] Wing Hang Leung,[1] Sophie Valkenburg,[2,7,†] Malik Peiris,[2,†] Wenwei Tu,[1,†] Yu Lung Lau,[1,†]

[1] Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong, China
[2] School of Public Health, The University of Hong Kong, Hong Kong, China
[3] Sir William Dunn School of Pathology, University of Oxford, Oxford, United Kingdom
[4] State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong, China
[5] Research Institute for Bioresources and Biotechnology, Ishikawa Prefectural University, Nonoichi, Japan
[6] IRCCS, Humanitas Research Hospital, Milan, Italy
[7] Department of Microbiology and Immunology, Peter Doherty Institute for Infection and Immunity, University of Melbourne, Melbourne, Australia

Running Title: SARS-CoV-2 mRNA and inactivated vaccines in adolescents

Corresponding authors:

Sophie Valkenburg, BioMedSci, BSci(Hons), PhD
E-mail: sophiev@hku.hk

Malik Peiris, MBBS, DPhil
E-mail: malik@hku.hk

Wenwei Tu, MBBS, PhD
E-mail: wwtu@hku.hk

Yu Lung Lau, MBChB, MD(Hons)
E-mail: lauylung@hku.hk

Key words: COVID-19, vaccine, BNT162b2, CoronaVac, immunity, adolescent

Manuscript Word Count: 4,000

Tables and Figures: 6

*, denotes all co-first authors contributed equally and can list their names in any order they wish when citing this work
†, denotes all corresponding authors contributed equally and can list their names in any order they wish when citing this work

STATEMENT OF CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

STATEMENT OF CONTRIBUTION

Y.L. Lau conceptualized the study. Y.L. Lau, M. Peiris, W. Tu, W.H. Leung, D. Leung, J.S. Rosa Duque and X. Wang designed the study. Y.L. Lau led the acquisition of funding. Y.L. Lau, W. Tu, M. Peiris and S. Valkenburg supervised the project. S. Chan, D. Leung, X. Wang, X. Mu and S.M.S. Cheng, J.H.Y. Lam led the study administrative procedures. W.H.S. Wong provided software support. S. Chan, W.W.Y. Tso, P. Ip and W.H.S. Wong contributed to recruitment of participants. Y.L. Lau, J.S. Rosa Duque, and G.T. Chua provided clinical assessments and follow-up. D. Leung, S. Chan, J.H.Y. Lam, J.S. Rosa Duque, Y.L. Lau and G.T. Chua collected safety data. S.M.S. Cheng, S. Chaothai, K.K.H. Kwan, K.C.K. Chan, J.K.C. Li, L.L.H. Luk, L.C.H. Tsang and M. Peiris developed and performed S-RBD IgG, N IgG, sVNT and neutralization antibody assays. C.A. Cohen, A. Hachim, N. Kavian and S. Valkenburg developed and performed the S IgG, IgG avidity, S IgG Fcγ receptor IIIa-binding and ORF8 antibody assays. The specialised ORF8 protein was developed and provided by M. Mori. X. Wang, X. Mu, Y. Zhang and W. Tu developed and performed the T cell assays. D. Leung, J.H.Y. Lam, C.H. Cheang, T.K. Hung and W.H.S. Wong curated the data. D. Leung, J.H.Y. Lam, J.S. Rosa Duque and W.H.S. Wong analysed the data. D. Leung, J.S. Rosa Duque, S.M.S Cheng, Y.L. Lau and M. Peiris performed the vaccine efficacy extrapolation. D. Leung and J.S. Rosa Duque visualized the data. J.S. Rosa Duque, D. Leung, X. Wang, S.M.S. Cheng, C.A. Cohen, W.H.S. Wong, J.H.Y. Lam and S. Chan validated the data. J.S. Rosa Duque and D. Leung wrote the first draft as supervised by Y.L. Lau, with input from X. Wang, S.M.S. Cheng and C.A. Cohen. All authors reviewed and approved the final manuscript.

J.S. Rosa Duque, X. Wang, D. Leung, S.M.S. Cheng and C.A. Cohen contributed equally; co-first authorship order was determined solely by career necessity, and they are free to list their names first when citing this work.

Y.L. Lau, W. Tu, M. Peiris and S. Valkenburg jointly supervised this work; co-corresponding authorship order was determined solely by suggested point of contact, and they are free to list their names as the primary corresponding author when citing this work.

ABSTRACT

For SARS-CoV-2 vaccines, efficacy data for BNT162b2 but not CoronaVac are available in adolescents. Phase II/III studies focused on neutralizing antibody responses in adolescents, neglecting binding antibody and cellular responses that are also important against SARS-CoV-2. Therefore, we conducted a registered clinical study (NCT04800133) to establish immunobridging with various antibody and cellular immunity markers and to compare the immunogenicity and reactogenicity of these 2 vaccines in healthy adolescents. One-dose BNT162b2 outcomes were also assessed since it had been recommended in some localities due to the risk of myocarditis. Antibodies and T cell immune responses were non-inferior or similar in adolescents receiving 2 doses of BNT162b2 (BB, *N*=116) and CoronaVac (CC, *N*=123) versus adults after 2 doses of the same vaccine (BB, *N*=147; CC, *N*=141) but not in adolescents after 1 dose of BNT162b2 (B, *N*=116). CC induced SARS-CoV-2 nucleocapsid (N) and N C-terminal domain seroconversion in more adolescents than adults. Adverse reactions were mostly mild for both vaccines and more frequent for BNT162b2. We confirmed higher S, neutralizing, avidity and Fc receptor-binding antibody responses in adolescents receiving BB than CC. This is the first study to show similar induction of strong S-specific T cells by the 2 vaccines, in addition to N- and M-specific T cells induced by CoronaVac but not BNT162b2 in adolescents. The implications of the differential ability to induce S- and non-S-specific antibody and T cell responses on the durability of protection and protection against virus variants by BNT162b2 and CoronaVac, the 2 most used SARS-CoV-2 vaccines in the world, should be further investigated. Our results support the use of both vaccines in adolescents.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to cause significant morbidity, mortality and socioeconomic disruptions worldwide.[1] While acute COVID-19 infections in children result in fewer hospitalizations and deaths than adults, they can lead to serious complications, such as multisystem inflammatory syndrome in children (MIS-C).[2] COVID-19 also has profound negative impact on school attendance, neurodevelopment and mental health in the paediatric population.[3,4] Several vaccines against SARS-CoV-2, utilizing novel nucleoside-modified mRNA technologies and the conventional inactivated whole-virus platform, underwent an expeditious review process by the World Health Organization (WHO) and were deemed adequately safe and effective for emergency use.[5,6] Landmark phase 3 clinical trials reported efficacies of ~90-95% for the mRNA vaccine, BNT162b2, and ~50-85% for the inactivated whole virus vaccine, CoronaVac, against symptomatic COVID-19 in persons aged ≥16 and ≥18 years old, respectively.[7,8] The vaccine efficacy for 12 to 15-year-olds receiving BNT162b2 was 100% in a phase 3 study.[9] Another phase 2 trial demonstrated that the seroconversion rate for 2 doses of CoronaVac in ages 12-17 years old was 100% as well.[10]

Vaccine efficacy has been linked to markers of immunological response known as correlates of protection (COP) in many infectious diseases, including neutralizing antibody titres and levels of spike protein (S) IgG for symptomatic COVID-19.[11-14] However, host defence against the viral infection involves many constituents of the immune system acting synergistically and dynamically, rather than merely reflected by antibody neutralization or S IgG.[15,16] As examples, non-neutralizing binding antibodies may play a role in protecting against COVID-19 as the onset of efficacy coincides with the presence of binding antibodies and precedes neutralizing antibody production in mRNA vaccines.[17] Optimised antibody avidity and Fc receptor-binding are also implicated in superior potency of antibody cocktail treatments for

COVID-19.[18] Additionally, non-S SARS-CoV-2 structural proteins, such as the nucleocapsid (N) and membrane (M), are associated with antibody responses in convalescent patients, and in fact, the C-terminal domain of N (N-CTD) is more specific to SARS-CoV-2.[19-21] Therefore, studies on immunogenicity outcomes that include these components are necessary.

To prevent progression to severe illness, T cells also play a major role in orchestrating a focused spectrum of immune responses, such as directing apoptosis of infected cells and antibody germinal centre reactions for high-avidity class-switched responses.[22-24] This is evident from studies that show humans who have inborn errors of immunity affecting T cells suffer from more severe and fatal viral infections, including COVID-19.[25] Most studies that investigated cellular immunogenicity focused on S-specific T cell responses, but non-spike proteins are relatively conserved and immunodominant for T cell responses in natural infection.[26,27] Two recent studies also hinted at a role of pre-existing cross-reactive T cells aborting SARS-CoV2 infections by examining frequently tested healthcare workers or household contacts who remained PCR-negative.[28,29] Protection against asymptomatic infection likely involves immunity at the respiratory mucosa rather than peripheral blood, as a potent response is likely required to clear offending viral seeding rapidly.[30] Unfortunately, COPs remain difficult to define due to the types of specimens required for assessment, workload in sample preparation and the functional complexity of assays. Characterizing all these humoral and cellular constituents against S and non-spike proteins collectively in addition to neutralizing antibody titres alone are essential for our understanding about vaccine responses to whole-virus vaccines but were not included in previous studies. In a recent head-to-head evaluation, BNT162b2 induced higher neutralization antibody levels, avidity and Fc receptor-binding antibodies in healthy adults, while T cell responses against SARS-CoV2 structural proteins were greater for those who received CoronaVac, which also contains other structural proteins in addition to S.[31]

Achieving a comprehensive understanding of vaccine-induced humoral and cellular immune responses is important for future development and approval of novel immunization platforms and boosters. Comprehensive comparative immunogenicity analyses of different vaccines allow us to investigate the contribution of different arms of the immune system to vaccine efficacy. These studies are rare in younger age group.

Additionally, clinical trials and post-marketing surveillance reported adverse events (AEs), such as hypersensitivity reactions and Bell's palsy, which have sparked public concerns.[32,33] In adolescents, our group amongst others recently found an increased incidence of myocarditis/pericarditis as high as 1 in 3,000 second doses of BNT162b2 in male adolescents, prompting Hong Kong (HK) and the UK to recommend a single dose of BNT162b2 for adolescents only.[34-36] While mRNA vaccines are linked to frequent systemic adverse reactions (ARs), reactogenicity appeared to be milder for the inactivated COVID-19 vaccine.

In this study, we aimed to perform an immunobridging study showing the humoral and cellular immunogenicity in adolescents receiving 1 and 2 doses of BNT162b2 and 2 doses of CoronaVac are non-inferior to adults, especially to inform on the use of CoronaVac in children for which there are no efficacy and effectiveness data at the time of writing. We compared various humoral and cellular response outcomes in adolescents to BNT162b2 and CoronaVac head-to-head, which are the top 2 most used COVID-19 vaccines in the world.[37]

RESULTS

Enrolment of study participants. A total 658 volunteers were screened, of which 646 who provided consent, consisting of 309 adolescents and 337 adults at dose 1, respectively, were enrolled between 27 April 2021 and 23 October 2021 (Extended Data Fig. 1). Based on clinical history and serological screening, 26 were enrolled in separate prior infection and 93 in severe paediatric illness sub-studies. The present interim analysis focused on healthy participants. There were 239 adolescent (11-17 years old, mean=14.0, SD=1.7) and 288 adult (18-67 years old, mean=47.5, SD=7.5) participants (total *N*=527), with similar numbers who completed the 2-dose (BB for BNT162b2 and CC for CoronaVac) vaccination series (Extended Data Table 1). All were included in the reactogenicity and safety (healthy safety population; see Methods, and Protocol and Statistical Analysis Plan in Supplementary Information) analyses. Demographic characteristics were evenly distributed. The evaluable analysis population in this analysis included those uninfected as assessed at any study visits, with no major protocol deviations and had a valid immunogenicity result (see Methods; Extended Data Fig. 1). There were 223 adolescents and 166 adults in the evaluable analysis set for primary immunogenicity after 2 doses. The corresponding modified intention-to-treat analysis included 226 adolescents and 223 adults in the expanded analysis population (see Methods; Extended Data Fig. 1).

Humoral immunogenicity outcomes between adolescents and adults. For the primary humoral immunogenicity analysis, SARS-CoV-2 S IgG, S-RBD IgG by enzyme-linked immunosorbent assay (ELISA), surrogate virus neutralization test (sVNT), plaque reduction neutralization test (PRNT), S IgG avidity and S IgG Fcγ receptor IIIa (FcγRIIIa)-binding on ELISA were performed for healthy, uninfected adolescents who received BB or CC (see Methods). Since there had been an interim recommendation to vaccinate adolescents with only 1 dose of BNT162b2 as the primary series in HK and the UK due to the higher risk of

myocarditis after 2 doses, we also tested whether adolescent B was non-inferior. Evaluable adolescent BNT162b2 recipients achieved 100% S-RBD IgG seroconversion after a single dose, with geometric mean (GM) optical density-450 (OD450) and sVNT inhibition of 1.96 and 81.3% on day 21 after dose 1 and 2.64 and 97.1% on day 28 after dose 2, respectively (Table 1a). A high proportion (96.6%) of evaluable adolescent CC had positive S-RBD IgG after 2 doses, with GM OD450 value of 1.20 and GM sVNT inhibition of 71.2%. PRNT was performed for 60 BB and 64 CC age- and sex-matched adolescents, otherwise selected at random; GM for PRNT90 was 115 and 9.58 after BB and CC, respectively; GM for PRNT50 was 331 and 28.0 after BB and CC, respectively. In addition, these same 64 adolescent CC were also tested for N IgG and N-CTD IgG as secondary immunogenicity outcomes. N IgG and N-CTD IgG seropositivity in adolescent CC was high, at 98.4% and 92.2%, with GM OD450 of 1.72 and 2.09, while only 52.4% and 28.6% of 21 adult CC (GM OD450 of 0.77 and 0.92) selected at random were seropositive, respectively. S IgG, S IgG avidity and S IgG FcγRIIIa-binding were also performed, and the proportions of seropositivity were analogous to S-RBD IgG and sVNT (Table 1a). After BB and CC, GM avidity indices were 29.7% and 20.5%, and the GM OD450 results of S IgG FcγRIIIa-binding, which is associated with antibody cellular cytotoxicity, were 2.07 and 0.75, respectively.

Compared to adults, humoral responses for the same vaccines were non-inferior for evaluable adolescent BB when measured by S IgG (GMR 1.09, 95% CI 1.03-1.15), S-RBD IgG (GMR 0.97, 95% CI 0.92-1.02), sVNT (GMR 1.02, 95% CI 1.02-1.03), PRNT90 (GMR 1.77, 95% CI 1.11-2.83), PRNT50 (GMR 1.28, 95% CI 0.84-1.96), S IgG avidity (GMR 1.26, 95% CI 1.15-1.38) and S IgG FcγRIIIa-binding (GMR 1.07, 95% CI 1.03-1.12) (Fig. 1aii). Similarly, adolescents mounted non-inferior humoral responses after CC by S IgG (GMR 1.26, 95% CI 1.07-1.48), S-RBD IgG (GMR 1.00, 95% CI 0.86-1.17), sVNT (GMR 1.31, 95% CI 1.15-1.48), PRNT90 (GMR 1.24, 95% CI 0.97-1.57), PRNT50 (GMR 1.30, 95% CI 0.93-1.82), S IgG avidity

(GMR 1.72, 95% CI 1.50-1.97) and S IgG FcγRIIIa-binding (GMR 1.25, 95% CI 0.97-1.62) (Fig. 1aiii). Interestingly, for N IgG and N-CTD IgG, only a small proportion of adult CC seroconverted and thus non-inferior and superior for adolescent CC (N IgG: GMR 2.24, 95% CI 1.87-2.68; N-CTD IgG: GMR 2.27, 95% CI 1.82-2.82) (Fig. 1aiii). N and N-CTD IgG levels were significantly elevated in adolescent CC (GM OD450 1.72 and 2.09, respectively) compared to adult CC (GM OD450 0.77 and 0.92, respectively), both $P<0.0001$ (Table 1a) (Extended Data Fig. 2bii).

Adolescent B satisfied non-inferiority by S-RBD IgG (GMR 0.72, 95% CI 0.66-0.77), sVNT (GMR 0.86, 95% CI 0.84-0.88) and S IgG avidity (GMR 0.92, 95% CI 0.82-1.03), but not by S IgG (GMR 0.48, 95% 0.42-0.54), PRNT90 (GMR 0.22, 95% CI 0.14-0.35), PRNT50 (GMR 0.17, 95% CI 0.10-0.30) and S IgG FcγRIIIa-binding (GMR 0.58, 95% CI 0.52-0.65), which failed the non-inferiority criterion (Fig. 1ai). S-RBD IgG, sVNT, PRNT90 and PRNT50 were all significantly lower in adolescents than adults (GM OD450 1.96 vs 2.73, GM % inhibition 81.3% vs 94.9%, GM PRNT90 14.4 vs 64.6 and GM PRNT50 45.2 vs 259, respectively), all $P<0.0001$ (Table 1a) (Extended Data Fig. 2a). Despite satisfying non-inferiority for S-RBD IgG and sVNT, adolescent B was indeed inferior to adult BB on both tests. Non-inferiority testing repeated in the expanded analysis sets confirmed similar findings (Extended Data Table 2).

Cellular immunogenicity outcomes between adolescents and adults. Interferon-γ (IFN-γ)$^+$ and interleukin-2 (IL-2)$^+$ CD4$^+$ and CD8$^+$ T cells responses specific to S (and N and M for CC) were analyzed with intracellular cytokine staining on flow cytometry for 21-28 days post-dose 1 and 28 days post-dose 2 as primary outcomes (58B, 56 BB and 60 CC evaluable adolescents were included; see Methods). A majority (≥70%) of adolescents receiving either vaccine had a detectable response (using ≥0.005% frequency of cytokine-expressing cells and stimulation index (SI) >2, with DMSO used as the background negative control, as cut-off; see Methods) for

S-specific IFN-γ^+CD4$^+$ or IL-2$^+$CD4$^+$ T cells 28 days after 2 doses, respectively (Table 1b). In contrast, both IFN-γ^+CD8$^+$ and IL-2$^+$CD8$^+$ T cells specific to S were detectable in approximately half of adolescents receiving 2 doses of either vaccine. T cell responses to S after B and to SNM, N and M after CC are shown in Table 1b.

S-specific IFN-γ^+CD4$^+$, IL-2$^+$CD4$^+$ and IFN-γ^+CD8$^+$ T cell responses satisfied the non-inferior criterion for evaluable adolescent BB compared to adults (GMR 1.23, 95% CI 0.66-2.29; GMR 1.15, 95% CI 0.67-1.99; GMR 1.32, 95% CI 0.64-2.73, respectively) (Fig. 1bii). For adolescent CC compared to adults, SNM-specific (sum of responses to individual peptide pools) IL-2$^+$CD4$^+$, IFN-γ^+CD8$^+$ and IL-2$^+$CD8$^+$ (GMR 0.99, 95% CI 0.64-1.55; GMR 1.23, 95% CI 0.62-2.46; GMR 0.88, 95% CI 0.61-1.28, respectively), N-specific IFN-γ^+CD4$^+$, IL-2$^+$CD4$^+$, IFN-γ^+CD8$^+$ and IL-2$^+$CD8$^+$ (GMR 1.17, 95% CI 0.61-2.23; GMR 1.09, 95% CI 0.64-1.85; GMR 1.33, 95% CI 0.65-2.70; GMR 1.02, 95% CI 0.69-1.50, respectively), M-specific IFN-γ^+CD8$^+$ and IL-2$^+$CD8$^+$ T cells (GMR 1.25, 95% CI 0.66-2.35; GMR 0.95, 95% CI 0.66-1.37, respectively) were non-inferior (Fig. 1biii). The remainder of the cellular immunogenicity outcomes between adolescents and adults were inconclusive as the 95% CI limits were out of the non-inferiority margin of 0.60 and 1. All 4 S-specific T cell responses between adolescents and adults showed no detectable differences in any vaccine regimens, except for S-specific IFN-γ^+CD4$^+$ T cell response, which was lower in adolescent B than adult BB (Extended Data Fig. 3 and 3a, respectively). Similarly, the secondary analysis in the less stringent expanded analysis sets confirmed these findings of non-inferiority (Extended Data Table 3).

Immunogenicity assessments between BNT162b2 and CoronaVac in adolescents.

Antibody and T cell responses were compared between vaccines in evaluable adolescents at post-dose 1 and post-dose 2. CC elicited lower humoral responses than BB as measured by S

IgG (GM OD450 0.54 vs 1.21; GMR 0.44, 95% CI 0.40-0.49), S-RBD IgG (GM OD450 1.20 vs 2.64; GMR 0.46, 95% CI 0.41-0.50), sVNT (GM % inhibition 71.2% vs 97.1%; GMR 0.73, 95% CI 0.68-0.79), PRNT90 (GM PRNT90 9.58 vs 115; GMR 0.08, 95% CI 0.07-0.11), PRNT50 (GM PRNT50 28.0 vs 331; GMR 0.08, 95% CI 0.07-0.11), S IgG avidity index (GM % avidity 20.5% vs 29.7%; GMR 0.69, 95% CI 0.63-0.76) and S IgG FcγRIIIa-binding (GM OD450 0.75 vs 2.07; GMR 0.36, 95% CI 0.31-0.42), all P<0.0001 (Table 1a) (Fig. 2a). Cellular immunogenicity outcomes were not significantly different except the S-specific IL-2$^+$CD4$^+$ T cell response was lower for CC (0.015% vs 0.032%; GMR 0.45, 95% CI 0.28-0.72) 28 days after 2 doses, P=0.001 (Fig. 2b). Comparisons of N- and M- specific immunogenicity outcomes are not presented since CC but not BB induced non-spike responses, an expected finding.

Compared to their own baseline values, both evaluable BB and CC had significant increases in T cell responses for S-specific IFN-γ$^+$CD4$^+$ [BB GM fold rise (GMFR) 6.78, 95% CI 3.90-11.8; CC GMFR 3.99, 95% CI 2.35-6.78], IL-2$^+$CD4$^+$ (BB GMFR 7.20, 95% CI 4.84-10.7; CC GMFR 2.73, 95% CI 1.83-4.07) and IFN-γ$^+$CD8$^+$ T cells (BB GMFR 3.41, 95% CI 1.96-5.92; CC GMFR 3.49, 95% CI 1.98-6.15), respectively (all P<0.0001) (Fig. 3a). As expected, there were no significant N-specific T cell responses elicited in BB. Additionally, CC elicited significant T cell responses and GMFR for S-specific IL-2$^+$CD8$^+$ (1.49, 95% CI 1.06-2.10, P=0.023) (Fig. 3a), SNM-specific IFN-γ$^+$CD4$^+$ (3.58, 95% CI 2.35-5.44, P<0.0001), IL-2$^+$CD4$^+$ (2.73, 95% CI 2.02-3.69, P<0.0001) and IFN-γ$^+$CD8$^+$ (2.98, 95% CI 1.82-4.88, P<0.0001) (Fig. 3b), N-specific IFN-γ$^+$CD4$^+$ (3.60, 95% CI 2.30-5.63, P<0.0001), IL-2$^+$CD4$^+$ (3.95, 95% CI 2.71-5.75, P<0.0001) and IFN-γ$^+$CD8$^+$ (1.81, 95% CI 1.02-3.21, P=0.042) (Fig. 3c) and M-specific IL-2$^+$CD4$^+$ (1.45, 95% CI 1.06-2.00, P=0.022) (Fig. 3d), respectively.

Estimation of vaccine efficacies based on neutralization titres for BNT162b2 and CoronaVac in adolescents. Since neutralizing antibodies have been established as a correlate of protection in multiple studies, we correlated our data with vaccine efficacies (VE) against symptomatic COVID-19 by using PRNT90 results normalized to convalescent sera in evaluable adolescents after receiving BNT162b2 or CoronaVac by mathematical extrapolation as previously published by Khoury et al (see Methods).[12,38,39] One-dose BNT162b2 has been used as the primary series for adolescents in some localities, but not for adults or CoronaVac at any age, and therefore we included adolescent B, BB and CC only in this analysis. The mean neutralization levels of BB, CC and B were 2.39, 0.20 and 0.30, which extrapolated to 93%, 50% and 59% VEs, respectively, all of which fulfilled the WHO's recommended 50% VE threshold as effective for use against COVID-19 (Fig. 4).[40]

Reactogenicity and safety of BNT162b2 and CoronaVac in adolescents. For adolescents in the healthy safety population, pain at the injection site was the most common AR reported for both vaccines, which was significantly more for those who received BNT162b2 (*N*=116) than CoronaVac (*N*=123) (B: 89.7% vs C: 54.5%, *P*<0.0001; BB: 87.9% vs CC: 52.9%, *P*<0.0001) (Fig. 5). BNT162b2 was also associated with more reports of several other ARs. More participants had antipyretics use after either dose of BNT162b2 (B: 9.5% vs C: 1.6%, *P*=0.009; BB: 22.4% vs CC: 0.8%, *P*<0.0001). Twenty-six mild AEs and 4 moderate AEs were reported within 28 days after vaccination in adolescents (22 for BB and 8 for CC in total) (Extended Data Table 4). There was no serious adverse event (SAE) for either vaccine.

Correlation of assays, characteristics and haematological parameters in adolescents. As a secondary objective, we explored potential associations between the immunogenicity outcomes (see Methods) in evaluable adolescents after B (Extended Data Fig. 4a) and C

(Extended Data Fig. 4b). There was strong correlation within humoral (S IgG with S IgG FcγRIIIa-binding, and sVNT with PRNT50) and within cellular outcomes (S-specific IFN-γ^+CD4$^+$ with IL-2$^+$CD4$^+$ and IFN-γ^+CD8$^+$; IL-2$^+$CD8$^+$ with IFN-γ^+CD8$^+$) for both vaccines. There was no correlation between the humoral and cellular outcomes. We also explored associations between sVNT levels and baseline demographic, anthropometric (height, weight) and haematological variables (total white blood cell count, absolute lymphocyte count, haemoglobin concentration) after B or C, which yielded no significant findings (Extended Data Tables 5 and 6).

DISCUSSION

This study is the first to assess the immunogenicity profiles of 2 major platforms of vaccines against COVID-19 in adolescents. Overall, the data demonstrated that most antibody and T cell responses for 2 doses of mRNA-based BNT162b2 and inactivated CoronaVac vaccines in 11- to 17-year-old children were non-inferior compared to adults. Between vaccines, the antibody levels were higher for adolescent BB than CC. S-specific T cell responses after 2 doses were robust and similar in adolescents receiving either vaccine, and N- and M-specific T cells were detected after CoronaVac but not BNT162b2, due to the absence of these antigens in BNT162b2. Both vaccines were associated with transient, tolerable AR in this age group, which occurred more frequently for BNT162b2 than CoronaVac. This is the first study to show the T cell responses to COVID-19 vaccines in adolescents and the first to demonstrate that adolescents mounted far superior antibody responses against N compared to adults.

Approval of vaccines in younger age groups is key to the transition of the devastating pandemic to stable endemicity by preventing hospitalizations and reducing COVID-19 severity in vulnerable children. The pivotal phase 3 trial for BNT162b2 in adolescents tested for non-inferiority of neutralizing antibody titres to support extending authorization of use to this age group and found superior PRNT in adolescents versus young adults.[9] While our study was not powered to determine superiority, our finding of non-inferiority was consistent. The phase 2 licensing trial on CoronaVac did not formally test for non-inferiority; however, we also showed that PRNT GM titres was non-inferior, supporting the use of CoronaVac in adolescents in the absence of efficacy data. Due to a high incidence of myocarditis after 2 doses of BNT162b2 in young adults, especially male adolescents, the second dose for adolescents was held off in places such as HK and the UK when there was no effectiveness data to inform this policy.[34,35] It was therefore relevant to ask if a single dose of vaccine could be non-inferior to the adult 2-dose

schedule since adolescents mounted better antibody responses to 2 doses of vaccine. However, we found an inferior neutralizing antibody response in adolescents receiving a single dose of BNT162b2 to adults who received 2 doses. This implies that a single dose may not be as effective in reducing symptomatic COVID-19 and other measures to mitigate the risk of myocarditis, such as increased dosing interval, should be used.[41]

We demonstrated similar or non-inferior T cell response in adolescent vaccinees. While a COP has yet to be confirmed for protection against severe COVID-19, T cells are likely a key defence against disease progression.[16,42] The concept that T cell immunity can be important for controlling severe viral infections is not novel. Burnet proposed in 1968 that humoral immunity did not mediate the "eruptive stage of measles" as "measles follows its normal course" in patients with agammaglobulinemia.[43] This is confirmed for COVID-19 in patients with severe combined immunodeficiencies and have absent or a malfunctional T cell compartment, who showed a high rate of fatality, which was not observed in those with X-linked agammaglobulinemia.[25] In hepatitis B immunization, vaccine effectiveness remains potent many years after vaccination with long-lived T and B cell responses and vastly waned antibody titres.[44,45] Moreover, despite exponential differences in neutralizing antibody titres, vaccines of different platforms including mRNA, adenoviral vector and inactivated vaccines have been shown to produce potent T cell responses and very high effectiveness against hospitalization.[31,46-48] Multiple lines of evidence support the basis that T cells play a major role in mediating protection against severe COVID-19.[49] Therefore, our T cell results suggest adolescents receiving either vaccine are also protected from severe COVID-19.

There were few studies that investigated immunogenicity between the mRNA and inactivated vaccines by direct comparison. In adults, BNT162b2 induced the strongest neutralizing antibody response on sVNT, followed by the adenovirus viral vector vaccines ChAdOx1/nCoV-19 and then Gam-COVID-Vac, and lastly the inactivated BBIBP-CorV. This

pattern of antibody response was similar across many other variants of concern tested.[50] Another study in adults involving our group also found BNT162b2 elicited higher neutralizing antibody titres, antibody Fc receptor binding and antibody avidity than CoronaVac, while 20 of 49 (40.8%) from the CoronaVac group had N-CTD IgG on ELISA.[31] In line with the stronger S IgG responses, our study observed that a similar 6/21 (28.6%) of adults, but a majority (59/64, 92.2%) of adolescents, developed IgG against N-CTD. N-CTD is responsible for type I interferon antagonism of the N protein.[21] CoronaVac appeared to elicit greater $CD4^+$ and $CD8^+$ T cell responses against the SARS-CoV2 structural peptide pool than BNT162b2 in a small group of adults,[31] and we also observed N- and M-specific T cell responses in adolescents receiving CC.

In this study, every participant was evaluated and followed by physicians and nurses, supported by an online AR reporting system. Despite its reliable approach, there were several limitations, such as the unblinded, non-randomized design. Our intended objective was to assess the results of a real-life, practical approach. Because of the non-randomized design, there is potential for selection bias. However, age and sex were similar between participants receiving both vaccines and we expect that the comparisons of immunogenicity are valid. Transmission of COVID-19 has been aggressively contained by the HK Government, with close contact tracing and quarantine measures, which precluded differentiation of the clinical efficacies of the 2 vaccines. However, immunobridging data are important, and we were able to estimate clinical efficacy based on neutralizing antibodies COP. Finally, this study did not assess immunogenicity against variants of concern (VOC), such as the newly emerged B.1.1.529 (Omicron) variant, which will be an important future step.

There is a major concern that Omicron's multiple S mutations may allow its escape from immunity after natural infection or vaccination. Multiple reports suggested 2 doses of BNT162b2 and CoronaVac failed to generate Omicron-neutralizing antibodies in a majority of

adults.[51] A BNT162b2 booster elicits neutralizing antibodies in most adults, although their durability may be limited.[52] In contrast, several studies found that T cell responses against the Omicron S protein are largely preserved (>80%) in most vaccinated and previously infected adults.[48,53-57] This lasting cellular immunity is one of many possibilities that contributes to the high (70%) clinical effectiveness of 2 doses of BNT162b2 doses against hospitalization during the initial Omicron wave.[58] Since this study showed that vaccine-induced T cell responses in adolescents are similar to adults, it is likely that their T cell responses remain protective against VOCs, including Omicron. We speculate that immunization platforms, such as the inactivated vaccines or multivalent peptide vaccines, which contain more conserved coronavirus protein antigens other than S, could be less susceptible to T cell escape and reduced clinical effectiveness against hospitalization.[59]

Taken together, vaccination elicits robust immune responses and remains a key method for providing host protection against COVID-19 in adolescents. Recipients of CoronaVac appear to mount lower antibody titres than BNT162b2. Our group had previously shown that intradermal administration of inactivated influenza vaccine can enhance immune responses, and whether this vaccination route induces higher humoral responses against SARS-CoV-2 and its VOCs should be explored for CoronaVac, which is especially important for countries where mRNA vaccines are not available.[60]

ONLINE METHODS

Study Design. Coronavirus disease-19 (COVID-19) Vaccination in Adolescents and Children (COVAC) is a registered clinical study (Department of Health, Hong Kong (HK), Clinical Trial Certificate 101894; clinicaltrials.gov NCT04800133) with a non-inferiority, non-blinded, non-randomized design aimed at establishing immunobridging for 2 COVID-19 vaccines, BNT162b2 (B) and CoronaVac (C), in children and comparing the reactogenicity and immunogenicity between the 2 vaccines in children. The research protocol and procedures were approved by the University of Hong Kong (HKU)/HK West Cluster Hospital Authority Institutional Review Board (UW21-157) and in compliance with the October 2013 Declaration of Helsinki principles, which were performed at a community vaccination centre (CVC) supported by HKU under the government's COVID-19 immunization program.

Participants. This analysis included 11- to 17-year-old children and ≥18-year-old adults. Recruitment targeted schoolchildren across HK. Potential participants needed to be healthy or in stable health condition, and those with known history of COVID-19, history of severe allergy, significant neuropsychiatric conditions, immunocompromised states, transfusion of blood products within 60 days, haemophilia, pregnancy or breastfeeding were excluded from this analysis.

Procedures. Potential participants were recruited via schools, mass media or referral. Study physicians provided information to participants and their parents/legally acceptable representatives (LARs), obtained informed consent from participants aged 18 years or above, or for underage participants, from their parents and LARs. Assent was also obtained from underage participants. Peripheral blood was then taken before each dose, 4 weeks after the

second-dose B (BB) and second-dose C (CC). The 2 doses of B and C were given 21-28 and 28-35 days apart, respectively.

Safety data collection

Participants were observed by study nurse(s) for 30 minutes after receiving the vaccine and attended by study physician(s) if clinically indicated. The study protocol required their recording of no or any prespecified adverse reactions (ARs) in an online or paper-based diary for 7 days. Adverse events (AEs) not included in the list were to be manually reported up to 28 days. Severe adverse events (SAEs), i.e., hospitalizations, life-threatening complications, disabilities, deaths and birth defects of their offspring, breakthrough COVID-19 infections, would be followed for 3 years. These cases were reviewed by the study physicians, who determined the possibility of clinical relevance to the study vaccine.

S-RBD IgG, N and N-CTD IgG, surrogate virus neutralization assay (sVNT) and plaque reduction neutralization test (PRNT)

Peripheral clotted blood was drawn, and the serum was stored at -80° C after separation. The SARS-CoV-2 S receptor-binding domain (S-RBD) IgG enzyme-linked immunosorbent assay (ELISA) and PRNT were carried out as previously described and validated.[61] sVNT was conducted according to the manufacturer's instructions (GenScript Inc, Piscataway, USA) and as described in our previous publication.[38,61] All sera were heat-inactivated at 56° C for 30 minutes before testing.

In brief, S-RBD IgG ELISA plates were coated overnight with 100 ng/well of purified recombinant S-RBD in PBS buffer, followed by addition of 100 μL Chonblock Blocking/Sample Dilution (CBSD) ELISA buffer (Chondrex Inc, Redmond, USA). This was incubated at room temperature (RT) for 2 hours. Serum was tested at a dilution of

1:100 in CBSD ELISA buffer, then added to the wells for 2 hours at 37°C. After washing with PBS containing 0.1% Tween 20, horseradish peroxidase (HRP)-conjugated goat anti-human IgG (1:5,000) (GE Healthcare, Chicago, USA) was added for 1 hour at 37°C, followed by washing five times with PBS containing 0.1% Tween 20. HRP substrate (Ncm TMB One, New Cell & Molecular Biotech Co. Ltd, China) of 100 μL was added for 15 minutes, and the reaction was stopped by 50 μL of 2 M H_2SO4. The OD was analysed in a Sunrise absorbance microplate reader (Tecan, Männedorf, Switzerland) at 450 nm wavelength. The background OD in PBS-coated control wells with the participant's serum was subtracted from each OD reading. Values at or above an OD450 of 0.5 were considered positive and values below were imputed as 0.25.

For N and N-CTD IgG, 96-well ELISA plates (Nunc MaxiSorp, Thermo Fisher Scientific) were first coated overnight with 125 ng (full length N) or 40.3 ng (N-CTD) per well of purified recombinant protein in PBS buffer. The plates were then blocked with 100 μl of Chonblock blocking/sample dilution ELISA buffer (Chondrex Inc, Redmon, US), followed by incubation at room temperature for 1 h. Each human plasma sample was diluted to 1:100 in Chonblock blocking/sample dilution ELISA buffer. Each sample was then added into the ELISA plates for a two-hour incubation at 37°C. After extensive washing with PBS containing 0.1% Tween 20, each well in the plate was further incubated with the anti-human IgG secondary antibody (1:2500, Thermo Fisher Scientific) for 1 hour 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 H2SO4 solution and analyzed on an absorbance microplate reader at 450 nm wavelength.

The sVNT was performed using 10 μL of each serum, positive and negative controls, which were diluted at 1:10 and mixed with an equal volume HRP conjugated to the SARS-CoV-2 S-RBD) (6 ng). The mixture was incubated for 30 minutes at 37°C, then 100 μL of each sample was added to microtitre plate wells coated with angiotensin-converting enzyme-2 (ACE-2) receptor. This plate was sealed for 15 minutes at 37°C and then washed with wash-solution, tapped dry, and 100 μL of 3,3',5,5'-tetramethylbenzidine (TMB) was added and incubated in the dark at RT for 15 minutes. This reaction was terminated using 50 μL of Stop Solution and the absorbance was read at 450 nm in a microplate reader. After confirming the positive and negative controls provided the recommended OD450 values, the % inhibition of each serum was calculated as (1 - sample OD value/negative control OD value) x100%. Inhibition (%) of at least 30%, the limit of quantification (LOQ), was regarded as positive, and values below 30% were imputed as 10%.

The PRNT was performed in duplicate using culture plates (Techno Plastic Products AG, Trasadingen, Switzerland) in a biosafety level 3 facility. Serial serum dilutions from 1:10 to at least 1:320 were incubated with ~30 plaque-forming units of SARS-CoV-2 BetaCoV/Hong Kong/VM20001061/2020 virus for 1 hour at 37°C. The virus-serum mixtures were added on to Vero-E6 cell monolayers and incubated for 1 hour at 37°C in a 5% CO_2 incubator. The plates were overlaid with 1% agarose in cell culture medium and incubated for 3 days when the plates were fixed and stained. Antibody titres were defined as the reciprocal of the highest serum dilution that resulted in >90% (PRNT90, a more stringent cut-off) or >50% (PRNT50) reduction in the number of plaques. Values below the lowest dilution tested (10) were imputed as 5 and those above 320 were imputed as 640.

S IgG, avidity and FcγRIIIa-binding

Detection of S IgG, avidity and FcγRIIIa-binding was carried out with reference to previous experiments.[31] Briefly, plates (Nunc MaxiSorp, Thermofisher Scientific) were coated with 250 ng/ml SARS-CoV-2 S protein (SinoBiological) overnight or 300 ng/mL ORF8 (Masashi Mori, Ishiwaka University, Japan) at 37°C for 2 hours.[19,62] The plates were blocked with 1% FBS in PBS for 1 hour, then incubated with 1:100 heat-inactivated (HI) serum diluted in 0.05% Tween-20/ 0.1% FBS in PBS for 2 hours at room temperature before rinsing again. To assess antibody avidity, plates were washed 3 times with 8M Urea before incubation for 2 hours with IgG-HRP (1:5000; G8-185, BD). HRP was revealed by stabilized hydrogen peroxide and tetramethylbenzidine (R&D systems) for 20 minutes, stopped with 2N H2SO4 and analysed with an absorbance microplate reader at 450 nm wavelength (Tecan Life Sciences). To measure FcγRIIIa-binding antibodies, plates were instead coated with 500ng/mL S protein, incubated with HI serum at 1:50 dilution for 1 hour at 37°C and then with biotinylated FcγRIIIa-V158 developed in-house at 100 ng/ml for 1 hour at 37°C. Streptavidin-HRP (1:10,000, Pierce) was then used to detect presence of S specific FcγRIIIa-V158-binding antibodies. OD450 values at or above the respective limits of detection (LODs) were considered positive, and values below were imputed as 0.5 of the LOD. The IgG avidity index was given by the ratio of the OD450 values post-washing to pre-washing of the plates, which was only calculated when associated with a positive S IgG value and this was censored at 100%.

T cell responses

Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood by density gradient separation then frozen in liquid nitrogen until use. Thawed PBMCs

were rested for 2 hours in 10% human AB serum supplemented RPMI medium. Next, the cells were stimulated with DMSO or 1 μg/mL overlapping peptide pools representing the SARS-CoV-2 S1/S2 subunits (StemCell Technologies, Vancouver, Canada), nucleocapsid (N) or membrane (M) proteins (Miltenyi Biotec, Bergisch Gladbach, Germany) for 16 hours in the presence of 1 μg/mL anti-CD28 and anti-CD49d costimulatory antibodies (clones CD28.2 and 9F10, Biolegend, San Diego, USA). After 2 hours of stimulation, 10 μg/mL brefeldin A (Sigma, Kawasaki, Japan) was added.[63] The cells were then washed and subjected to immunostaining using a fixable viability dye (eBioscience, Santa Clara, USA, 1:60) and antibodies against $CD3^+$ (HIT3a, 1:60), $CD4^+$ (OKT4, 1:60), $CD8^+$ (HIT8a, 1:60), IFN-γ (B27, 1:15) and IL-2 (MQ1-17H12, 1:15) antibodies (Biolegend, San Diego, USA). Data acquisition was carried out using flow cytometry (LSR II; BD Biosciences, Franklin Lakes, USA) and analyzed by Flowjo v10 software (BD, Ashland, USA). The antigen-specific T cells were calculated by subtracting the background (DMSO) data.[64] T cell response was considered positive when the frequency of cytokine-expressing cells was higher than 0.005% and the stimulation index was higher than 2. Negative values were imputed as 0.0025%.

Outcomes. The primary immunogenicity outcomes included: S-specific antibody markers, which were the S IgG and S-RBD IgG levels, sVNT %inhibition, 90% and 50% PRNT titres, S IgG avidity and FcγRIIIa-binding; S-specific (and N- and M-specific for CC) IFN-γ^+ and IL-2^+ $CD4^+$ and $CD8^+$ T cell responses measured by the flow-cytometry-based intracellular cytokine staining assay; at 21 days post-dose 1 (or 28 days for CC) and 28 days after 2 doses at a prime-boost interval of 21 days (for BB) or 28 (for CC). The primary reactogenicity outcomes were solicited ARs and anti-pyretic use for 7 days after each vaccine dose.

Secondary immunogenicity outcomes included N and N-CTD IgG levels in CC recipients. For safety, the secondary outcomes were unsolicited AEs reported 28 days after each dose and SAEs collected throughout the study period. Other secondary outcomes not included in this interim analysis, such as the evaluation of similar outcomes in participants with severe paediatric illnesses, can be found in the Protocol and Statistical Analysis Plan (Supplementary Materials).

Statistical Analyses.

Sample size and power estimation

Power analyses were performed using G*Power (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) and Sampsize (sampsize.sourceforge.net). For primary immunogenicity objectives, when comparing the peak geometric mean (GM) immunogenicity outcomes of children with that of parents, or between vaccine types, a sample size of 61 in each group would assure that a two-sided test with α=0.05 has 99% power to detect an effect size with a Cohen's d value=0.78, or a difference of 0.51 after natural log transformation, between 2 groups and a standard deviation (SD) of 0.65 on the natural log scale within each group. For assays with higher technical requirements such as PRNT, 66 evaluable adolescents and 16 evaluable adults tested would achieve 80% power to detect the same difference with the same α and SD. For the proportion of participants with a positive result in immunogenicity outcomes or ARs, 110 adolescents would yield a 95% chance to detect the true value within $\pm$7.5% of the measured percentage, assuming a prevalence of 80%. Recruitment of 120 adolescents were targeted per vaccine type to accommodate for attrition.

Analysis sets

582 The primary analysis of humoral and cellular immunogenicity outcomes was
583 performed in healthy participants on a per-protocol basis. The evaluable analysis
584 population included participants who were uninfected during the first 3 study visits
585 (based on clinical history, baseline S-RBD IgG negativity, N and ORF8 IgG negativity),
586 generally healthy with no major protocol deviations, blood sampling within the evaluable
587 window for post-dose 1 (no more than 3 days earlier or later than day 21 for B or day 28
588 for C, and before dose 2) or post-dose 2 time-points (within day 14-42 post-dose 2 and
589 before any further doses), and had a valid result for the relevant analysis and timepoint
590 (see protocol in Supplementary Information). The expanded analysis population
591 included similar criteria as the evaluable population except the notable differences of the
592 requirement of a valid immunogenicity result for the particular analysis at least 14 days
593 post-dose 1 but before dose 2 and between 7-56 days post-dose 2 (see protocol in
594 Supplementary Information). The non-inferiority hypothesis testing for primary
595 immunogenicity outcomes included participants aged ≥18 years in the adult group and
596 11-17 years in the adolescent group. GMs were calculated for each immunogenicity
597 outcome, time-point and subgroup. GM ratios (GMRs) were calculated as exponentiated
598 differences between the means of the natural log-transformed immunogenicity outcomes
599 in the adolescent group and adult reference group. The GMRs were reported with a
600 two-sided 95% CI for testing the non-inferiority hypothesis at the margin of 0.60. Non-
601 inferiority analyses were repeated on modified intention-to-treat basis in the expanded
602 analysis sets, which also included more participants in a broader dosing and blood
603 sampling intervals. Analysis subgroups were considered superior if the lower bound of
604 the 95% CI for GMR with the comparator was >1, inferior if the upper bound was <1, and
605 inconclusive if both criteria for superiority and inferiority were met. The proportion of
606 participants in each subgroup with a positive result (at or above the LOD, LOQ or cut-off)

for a test at a particular time-point was reported in percentage with a 95% CI calculated by the Clopper-Pearson method. Comparisons of proportions were performed by the Fisher exact test. Immunogenicity outcome data below the cut-off were imputed with half the cut-off value. Comparisons of immunogenicity outcomes between groups were made by unpaired t test after natural log transformation.

As a secondary immunogenicity analysis, correlations between primary immunogenicity outcomes were evaluated by Pearson correlation coefficients after natural log transformation, with a more stringent significance level of P=0.01 to account for multiple comparison testing. Relationships between sVNT %inhibition and baseline variables such as age, sex and haematological parameters were explored by multiple linear regression post-dose 1 by vaccine type in the adolescent group only at P=0.01.

Reactogenicity and safety analyses were conducted in healthy, uninfected participants who reported any safety or AR data in the adolescent group, and these comprised the healthy safety population. For the primary reactogenicity analysis, the proportion of types and severity of solicited ARs and antipyretic use within 7 days post-doses 1 and 2 are presented in percentages with the 95% CI calculated by the Clopper-Pearson method. The presence of each AR (regardless of severity) and antipyretic use was compared between vaccine types by the Fisher exact test. Incidences of AEs and SAEs reported by the 3rd study visit (28 days post-dose 2) are shown as a total number and events-per-participant by vaccine type.

Vaccine efficacy estimation

As a secondary objective, vaccine efficacies (VEs) were estimated by correlation with neutralizing antibody titres as previously established.[12] The mean neutralizing levels (fold of convalescent) were derived by dividing the GMTs of PRNT90 in healthy

evaluable adolescents receiving B, BB and CC with that of 102 convalescent sera collected on days 28-59 post-onset of illness in patients aged ≥18 years.[38,39] A single point estimate of VE was obtained for each vaccination by extrapolating the best fit of the logistic model, which was generated using an online plot digitizer tool (https://automeris.io/WebPlotDigitizer/, version 4.5).

FUNDING

This study was supported by the research grant, COVID19F02, from the Food and Health Bureau of the Government of Hong Kong, which was not involved in the study design, data collection, laboratory assays, statistical computation, interpretation or final conclusions of this project.

ACKNOWLEDGEMENTS

We thank the personnel from the HKUMed CVC at Ap Lei Chau Sports Centre and Gleneagles Hospital HK, particularly Dr Victoria WY Wong of HKU, Ms Cindy HS Man and Dr Hon-Kuan Tong who operated the territory-wide vaccination programme at the CVC and assisted in clinical monitoring of vaccine recipients alongside our group. The investigators are grateful to all clinical research team members and laboratory staff of Department of Paediatrics and Adolescent Medicine, including Mr KW Chan and Dr Davy CW Lee, for their research support. We are thankful to Dr Pamela P Lee at HKU and Dr Kai Ning Cheong at Hong Kong Children's Hospital who gave input to the study. We are indebted to the participants who have placed their trust in the investigators and joined the study.

DATA AVAILABILITY

The study's Protocol and Statistical Analysis Plan are contained in the Supplementary Information. To protect the confidentiality of participants, only deidentified participant-level datasets will be shared to researchers who provide a scientifically valid proposal. Since this study is ongoing, data will be available upon request 1 month after the completion of the study (anticipated in 2025). Enquiries can be addressed to lauylung@hku.hk.

REFERENCES

1. Johns Hopkins Coronavirus Resource Center. (https://coronavirus.jhu.edu/map.html).

2. Smith, C.*, et al.* Deaths in children and young people in England after SARS-CoV-2 infection during the first pandemic year. *Nat Med* (2021).

3. Tso, W.W.Y.*, et al.* Vulnerability and resilience in children during the COVID-19 pandemic. *Eur Child Adolesc Psychiatry* (2020).

4. Tso, W.W.Y.*, et al.* Mental health & maltreatment risk of children with special educational needs during COVID-19. *Child Abuse & Neglect*, 105457 (2022).

5. World Health Organization. Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing. *https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1* (2021).

6. World Health Organization. Interim recommendations for use of the inactivated COVID-19 vaccine, CoronaVac, developed by Sinovac. *https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-Sinovac-CoronaVac-2021.1* (2021).

7. Polack, F.P.*, et al.* Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* **383**, 2603-2615 (2020).

8. Tanriover, M.D.*, et al.* Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *The Lancet* **398**, 213-222 (2021).

9. Frenck, R.W., Jr.*, et al.* Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. *N Engl J Med* **385**, 239-250 (2021).

10. Han, B.*, 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. *The Lancet Infectious Diseases* **21**, 1645-1653 (2021).

11. Plotkin, S.A. Vaccines: correlates of vaccine-induced immunity. *Clin Infect Dis* **47**, 401-409 (2008).

12. Khoury, D.S.*, et al.* Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* **27**, 1205-1211 (2021).

13. Earle, K.A.*, et al.* Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine* **39**, 4423-4428 (2021).

14. Bergwerk, M.*, et al.* Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. *N Engl J Med* **385**, 1474-1484 (2021).

15. Sette, A. & Crotty, S. Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell* **184**, 861-880 (2021).

16. Rydyznski Moderbacher, C.*, et al.* Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. *Cell* **183**, 996-1012 e1019 (2020).

17. Kalimuddin, S.*, et al.* Early T cell and binding antibody responses are associated with COVID-19 RNA vaccine efficacy onset. *Med (N Y)* **2**, 682-688 e684 (2021).

18. Yamin, R.*, et al.* Fc-engineered antibody therapeutics with improved anti-SARS-CoV-2 efficacy. *Nature* **599**, 465-470 (2021).

19. Hachim, A.*, et al.* ORF8 and ORF3b antibodies are accurate serological markers of early and late SARS-CoV-2 infection. *Nat Immunol* **21**, 1293-1301 (2020).

20. Hachim, A.*, et al.* The SARS-CoV-2 antibody landscape is lower in magnitude for structural proteins, diversified for accessory proteins and stable long-term in children. *medRxiv* (2021).

21. Wu, C.*, et al.* Characterization of SARS-CoV-2 nucleocapsid protein reveals multiple functional consequences of the C-terminal domain. *iScience* **24**, 102681 (2021).

22. Kalfaoglu, B., Almeida-Santos, J., Tye, C.A., Satou, Y. & Ono, M. T-Cell Hyperactivation and Paralysis in Severe COVID-19 Infection Revealed by Single-Cell Analysis. *Front Immunol* **11**, 589380 (2020).

23. Juno, J.A.*, et al.* Humoral and circulating follicular helper T cell responses in recovered patients with COVID-19. *Nat Med* **26**, 1428-1434 (2020).

24. Koutsakos, M.*, et al.* Integrated immune dynamics define correlates of COVID-19 severity and antibody responses. *Cell Rep Med* **2**, 100208 (2021).

25. Bucciol, G., Tangye, S.G. & Meyts, I. Coronavirus disease 2019 in patients with inborn errors of immunity: lessons learned. *Curr Opin Pediatr* **33**, 648-656 (2021).

26. Grifoni, A.*, et al.* Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. *Cell* **181**, 1489-1501 e1415 (2020).

27. Grifoni, A.*, et al.* SARS-CoV-2 human T cell epitopes: Adaptive immune response against COVID-19. *Cell Host Microbe* **29**, 1076-1092 (2021).

28. Swadling, L.*, et al.* Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2. *Nature* **601**, 110-117 (2022).

29. Kundu, R.*, et al.* Cross-reactive memory T cells associate with protection against SARS-CoV-2 infection in COVID-19 contacts. *Nature Communications* **13**(2022).

30. Hassan, A.O.*, et al.* A Single-Dose Intranasal ChAd Vaccine Protects Upper and Lower Respiratory Tracts against SARS-CoV-2. *Cell* **183**, 169-184 e113 (2020).

31. Mok, C.K.P.*, et al.* Comparison of the immunogenicity of BNT162b2 and CoronaVac COVID-19 vaccines in Hong Kong. *Respirology* (2021).

32. Fiolet, T., Kherabi, Y., MacDonald, C.J., Ghosn, J. & Peiffer-Smadja, N. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. *Clin Microbiol Infect* (2021).

33. Wan, E.Y.F.*, et al.* Bell's palsy following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and nested case-control study. *The Lancet Infectious Diseases* **22**, 64-72 (2022).

34. Chua, G.T., *et al.* Epidemiology of Acute Myocarditis/Pericarditis in Hong Kong Adolescents Following Comirnaty Vaccination. *Clin Infect Dis* (2021).

35. Dagan, N., Barda, N. & Balicer, R.D. Adverse Effects after BNT162b2 Vaccine and SARS-CoV-2 Infection, According to Age and Sex. *N Engl J Med* **385**, 2299 (2021).

36. Scientific Committee on Emerging and Zoonotic Diseases and Scientific Committee on Vaccine Preventable Diseases, Centre for Health Protection, Department of Health, the Government of Hong Kong. Consensus Interim Recommendations on the Use of COVID-19 Vaccines in Hong Kong (As of 15 September 2021). *https://www.chp.gov.hk/files/pdf/consensus_interim_recommendations_on_the_use_of_covid19_vaccines_in_hk_15sept21.pdf*.

37. Mallapaty, S. China's COVID vaccines have been crucial — now immunity is waning. *Nature* **598**, 398-399 (2021).

38. Lau, E.H.Y., *et al.* Neutralizing antibody titres in SARS-CoV-2 infections. *Nat Commun* **12**, 63 (2021).

39. Lau, E.H., *et al.* Long-term persistence of SARS-CoV-2 neutralizing antibody responses after infection and estimates of the duration of protection. *EClinicalMedicine* **41**, 101174 (2021).

40. Hodgson, S.H., *et al.* What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. *The Lancet Infectious Diseases* **21**, e26-e35 (2021).

41. Buchan, S.A., *et al.* Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval. *medRxiv* (2021).

42. Mathew, D., *et al.* Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. *Science* **369**(2020).

43. Burnet, F.M. Measles as an index of immunological function. *Lancet* **292**, 610-613 (1968).

44. Coursaget, P., *et al.* Twelve-year follow-up study of hepatitis B immunization of Senegalese infants. *Journal of Hepatology* **21**, 250-254 (1994).

45. Simons, B.C., *et al.* A Longitudinal Hepatitis B Vaccine Cohort Demonstrates Long-lasting Hepatitis B Virus (HBV) Cellular Immunity Despite Loss of Antibody Against HBV Surface Antigen. *J Infect Dis* **214**, 273-280 (2016).

46. Jara, A., *et al.* Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. *N Engl J Med* **385**, 875-884 (2021).

47. Lopez Bernal, J., *et al.* 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 (2021).

48. GeurtsvanKessel, C.H., *et al.* Divergent SARS CoV-2 Omicron-specific T- and B-cell responses in COVID-19 vaccine recipients. *medRxiv* (2021).

49. Peng, Y., *et al.* An immunodominant NP105-113-B*07:02 cytotoxic T cell response controls viral replication and is associated with less severe COVID-19 disease. *Nat Immunol* **23**, 50-61 (2022).

50. Dashdorj, N.J.*, et al.* Direct comparison of antibody responses to four SARS-CoV-2 vaccines in Mongolia. *Cell Host Microbe* **29**, 1738-1743 e1734 (2021).

51. Lu, L.*, et al.* Neutralization of SARS-CoV-2 Omicron variant by sera from BNT162b2 or Coronavac vaccine recipients. *Clin Infect Dis* (2021).

52. Wilhelm, A.*, et al.* Reduced Neutralization of SARS-CoV-2 Omicron Variant by Vaccine Sera and Monoclonal Antibodies. *medRxiv* (2021).

53. Keeton, R.*, et al.* SARS-CoV-2 spike T cell responses induced upon vaccination or infection remain robust against Omicron. *medRxiv*, 2021.2012.2026.21268380 (2021).

54. De Marco, L.*, et al.* Preserved T cell reactivity to the SARS-CoV-2 Omicron variant indicates continued protection in vaccinated individuals.
. *medRxiv* (2021).

55. Liu, J.*, et al.* Vaccines Elicit Highly Cross-Reactive Cellular Immunity to the SARS-CoV-2 Omicron Variant. *medRxiv* (2022).

56. Naranbhai, V.*, et al.* T cell reactivity to the SARS-CoV-2 Omicron variant is preserved in most but not all prior infected and vaccinated individuals. *medRxiv* (2022).

57. Tarke, A.*, et al.* SARS-CoV-2 vaccination induces immunological memory able to cross-recognize variants from Alpha to Omicron
. *medRxiv* (2021).

58. Collie, S., Champion, J., Moultrie, H., Bekker, L.G. & Gray, G. Effectiveness of BNT162b2 vaccine against Omicron variant in South Africa. *N Engl J Med* (2021).

59. Heitmann, J.S.*, et al.* A COVID-19 peptide vaccine for the induction of SARS-CoV-2 T cell immunity. *Nature* (2021).

60. Chiu, S.S., Chan, K.H., Tu, W., Lau, Y.L. & Peiris, J.S. Immunogenicity and safety of intradermal versus intramuscular route of influenza immunization in infants less than 6 months of age: a randomized controlled trial. *Vaccine* **27**, 4834-4839 (2009).

61. Perera, R.A.*, et al.* Serological assays for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), March 2020. *Euro Surveill* **25**(2020).

62. Imamura, T., Isozumi, N., Higashimura, Y., Ohki, S. & Mori, M. Production of ORF8 protein from SARS-CoV-2 using an inducible virus-mediated expression system in suspension-cultured tobacco BY-2 cells. *Plant Cell Rep* **40**, 433-436 (2021).

63. Sattler, A.*, et al.* Impaired humoral and cellular immunity after SARS-CoV-2 BNT162b2 (tozinameran) prime-boost vaccination in kidney transplant recipients. *J Clin Invest* **131**(2021).

64. Mateus, J.*, et al.* Low-dose mRNA-1273 COVID-19 vaccine generates durable memory enhanced by cross-reactive T cells. *Science* **374**, eabj9853 (2021).

TABLES

Table 1a. Humoral immunogenicity outcomes in evaluable immunogenicity populations by vaccine regimen.

	BNT162b2			CoronaVac	
	Adolescents 1 dose	Adolescents 2 doses	Adults 2 doses	Adolescents 2 doses	Adults 2 doses
Antibody responses					
S IgG on ELISA					
N	101	103	115	116	50
GM OD450 value (95% CI)	0.53 (0.47-0.60)	1.21 (1.17-1.25)	1.11 (1.07-1.16)	0.54 (0.49-0.58)	0.42 (0.36-0.50)
% positive (>/=LOD at 0.3)	100%, *P*>0.9999	100%, *P*>0.9999	99.1%	94.0%, *P*=0.0228	82.0%
S-RBD IgG on ELISA					
N	107	104	115	119	51
GM OD450 value (95% CI)	1.96 (1.83-2.09)	2.64 (2.53-2.75)	2.73 (2.63-2.83)	1.20 (1.10-1.31)	1.20 (1.04-1.37)
% positive (>/=LOD at 0.5)	100%, *P*>0.9999	100%, *P*>0.9999	100%	96.6%, *P*>0.9999	96.1%
S-RBD ACE2-blocking antibody on sVNT					
N	107	104	115	119	51
GM % inhibition (95% CI)	81.3% (79.2-83.5%)	97.1% (97.0-97.2%)	94.9% (94.3-95.5%)	71.2% (66.7-76.0%)	54.6% (48.5-61.4%)
% positive (>/=LOQ at 30%)	100%, *P*>0.9999	100%, *P*>0.9999	100%	96.6%, *P*=0.43	94.1%
Neutralizing antibody on PRNT					
N	63	60	13	64	19
GM PRNT90 (95% CI)	14.4 (11.9-17.4)	115 (93.3-140)	64.6 (43.5-96.1)	9.58 (8.50-10.8)	7.75 (6.35-9.46)
% positive (>/=LOD at 10)	85.7%, *P*=0.34	100%, *P*>0.9999	100%	75.0%, *P*=0.16	57.9%
GM PRNT50 (95% CI)	45.2 (36.1-56.5)	331 (277-396)	259 (168-398)	28.0 (23.9-32.8)	21.5 (15.4-30.0)
% positive (>/=LOD at 10)	98.4%, *P*>0.9999	100%, *P*>0.9999	100%	100%, *P*=0.23	94.7%
S IgG avidity on ELISA					
N	88	103	114	109	41
GM avidity index (95% CI)	21.5% (19.5-23.8)	29.7% (27.9-31.5)	23.5% (22.0-25.1)	20.5% (19.1-22.1)	12.0% (10.8-13.3)
S IgG FcγRIIIa-binding on ELISA					
N	101	103	115	116	50
GM OD450 value (95% CI)	1.12 (1.00-1.26)	2.07 (2.02-2.11)	1.93 (1.87-1.99)	0.75 (0.65-0.86)	0.60 (0.48-0.74)
% positive (>/=LOD at 0.28)	100%, *P*>0.9999	100%, *P*>0.9999	100%	87.1%, *P*=0.81	86.0%
N IgG on ELISA					
N	/	/	/	64	21
GM OD450 value (95% CI)	/	/	/	1.72 (1.61-1.83)	0.77 (0.59-0.99)
% positive (>/=LOD at 0.88)	/	/	/	98.4%, *P*<0.0001	52.4%
N-CTD IgG on ELISA					
N	/	/	/	64	21
GM OD450 value (95% CI)	/	/	/	2.09 (1.89-2.31)	0.92 (0.73-1.17)
% positive (>/=LOD at 1.34)	/	/	/	92.2%, *P*<0.0001	28.6%

GM, geometric mean; OD, optical density; LOD, limit of detection; LOQ, limit of quantification; CI, confidence interval; S, spike protein; ELISA, enzyme-linked immunosorbent assay; RBD, receptor-binding domain; ACE-2, angiotensin-converting enzyme-2; sVNT, surrogate virus neutralization test; PRNT, plaque reduction neutralization test; PRNT90, 90% plaque reduction neutralization titre; PRNT50, 50% plaque reduction neutralization titre; FcγRIIIa: Fc gamma receptor III-a; N, nucleocapsid protein; CTD, C-terminal domain; IFN-γ, interferon-gamma; IL-2, interleukin-2.

P-values compare the proportion of positive responses between adolescents receiving 1 or 2 doses of vaccine and adults receiving 2 doses of the same vaccine by Fisher's exact test.

Table 1b. Cellular immunogenicity outcomes in evaluable immunogenicity populations by vaccine regimen.

	BNT162b2			CoronaVac	
	Adolescents 1 dose	**Adolescents 2 doses**	**Adults 2 doses**	**Adolescents 2 doses**	**Adults 2 doses**
T cell responses					
S-specific T cell responses on flow cytometry					
N	58	56	47	60	36
GM % IFN-γ$^+$CD4$^+$ T cells (95% CI)	0.014% (0.009-0.021%)	0.041% (0.028-0.06%)	0.033% (0.020-0.056%)	0.023% (0.015-0.036%)	0.021% (0.011-0.039%)
% positive (>/=cut-off at 0.005%)	62.1%, *P*=0.21	83.9%, *P*=0.33	74.5%	70.0%, *P*=0.38	61.1%
GM % IL-2$^+$CD4$^+$ T cells (95% CI)	0.023% (0.016-0.033%)	0.032% (0.023-0.045%)	0.028% (0.018-0.044%)	0.015% (0.011-0.020%)	0.015% (0.010-0.024%)
% positive (>/=cut-off at 0.005%)	74.1%, *P*=0.82	85.7%, *P*=0.31	76.6%	73.3%, *P*=0.82	69.4%
GM % IFN-γ$^+$CD8$^+$ T cells (95% CI)	0.009% (0.006-0.014%)	0.018% (0.011-0.028%)	0.013% (0.008-0.024%)	0.014% (0.009-0.023%)	0.015% (0.007-0.029%)
% positive (>/=cut-off at 0.005%)	41.4%, *P*=0.69	57.1%, *P*=0.33	46.8%	48.3%, *P*=0.83	44.4%
GM % IL-2$^+$CD8$^+$ T cells (95% CI)	0.005% (0.004-0.007%)	0.005% (0.004-0.007%)	0.007% (0.005-0.010%)	0.006% (0.005-0.008%)	0.007% (0.004-0.010%)
% positive (>/=cut-off at 0.005%)	32.8%, *P*=0.11	44.6%, *P*=0.70	48.9%	48.3%, *P*=0.67	41.7%
Total S, N and M-specific T cell responses on flow cytometry					
N	/	/	/	60	36
GM % IFN-γ$^+$CD4$^+$ T cells (95% CI)	/	/	/	0.058% (0.041-0.083%)	0.068% (0.041-0.113%)
% positive (>/=cut-off at 0.01%)	/	/	/	83.3%, *P*=0.59	77.8%
GM % IL-2$^+$CD4$^+$ T cells (95% CI)	/	/	/	0.039% (0.030-0.052%)	0.040% (0.027-0.057%)
% positive (>/=cut-off at 0.01%)	/	/	/	83.3%, *P*=0.59	77.8%
GM % IFN-γ$^+$CD8$^+$ T cells (95% CI)	/	/	/	0.050% (0.033-0.077%)	0.041% (0.023-0.071%)
% positive (>/=cut-off at 0.01%)	/	/	/	65.0%, *P*=0.52	58.3%
GM % IL-2$^+$CD8$^+$ T cells (95% CI)	/	/	/	0.017% (0.014-0.022%)	0.020% (0.014-0.027%)
% positive (>/=cut-off at 0.01%)	/	/	/	58.3%, *P*>0.9999	58.3%
N-specific T cell responses on flow cytometry					
N	/	/	/	60	36
GM % IFN-γ$^+$CD4$^+$ T cells (95% CI)	/	/	/	0.011% (0.008-0.017%)	0.010% (0.006-0.016%)
% positive (>/=cut-off at 0.005%)	/	/	/	55.0%, *P*=0.68	50.0%
GM % IL-2$^+$CD4$^+$ T cells (95% CI)	/	/	/	0.013% (0.009-0.018%)	0.012% (0.008-0.018%)
% positive (>/=cut-off at 0.005%)	/	/	/	66.7%, *P*>0.9999	66.7%
GM % IFN-γ$^+$CD8$^+$ T cells (95% CI)	/	/	/	0.008% (0.005-0.012%)	0.006% (0.003-0.010%)
% positive (>/=cut-off at 0.005%)	/	/	/	31.7%, *P*=0.64	25.0%
GM % IL-2$^+$CD8$^+$ T cells (95% CI)	/	/	/	0.004% (0.003-0.005%)	0.004% (0.003-0.006%)
% positive (>/=cut-off at 0.005%)	/	/	/	28.3%, *P*=0.81	25.0%
M-specific T cell responses on flow cytometry					
N	/	/	/	60	36
GM % IFN-γ$^+$CD4$^+$ T cells (95% CI)	/	/	/	0.007% (0.005-0.010%)	0.009% (0.005-0.016%)
% positive (>/=cut-off at 0.005%)	/	/	/	36.7%, *P*=0.67	41.7%
GM % IL-2$^+$CD4$^+$ T cells (95% CI)	/	/	/	0.006% (0.004-0.007%)	0.006% (0.004-0.009%)
% positive (>/=cut-off at 0.005%)	/	/	/	46.7%, *P*>0.9999	47.2%
GM % IFN-γ$^+$CD8$^+$ T cells (95% CI)	/	/	/	0.006% (0.004-0.009%)	0.005% (0.003-0.008%)
% positive (>/=cut-off at 0.005%)	/	/	/	25.0%, *P*=0.62	19.4%
GM % IL-2$^+$CD8$^+$ T cells (95% CI)	/	/	/	0.004% (0.003-0.005%)	0.004% (0.003-0.006%)
% positive (>/=cut-off at 0.005%)	/	/	/	23.3%, *P*>0.9999	25.0%

GM, geometric mean; CI, confidence interval; IFN-γ, interferon-gamma; IL-2, interleukin-2.
P-values compare the proportion of positive responses between adolescents receiving 1 or 2 doses of vaccine and adults receiving 2 doses of the same vaccine by Fisher's exact test.

Fig. 1a

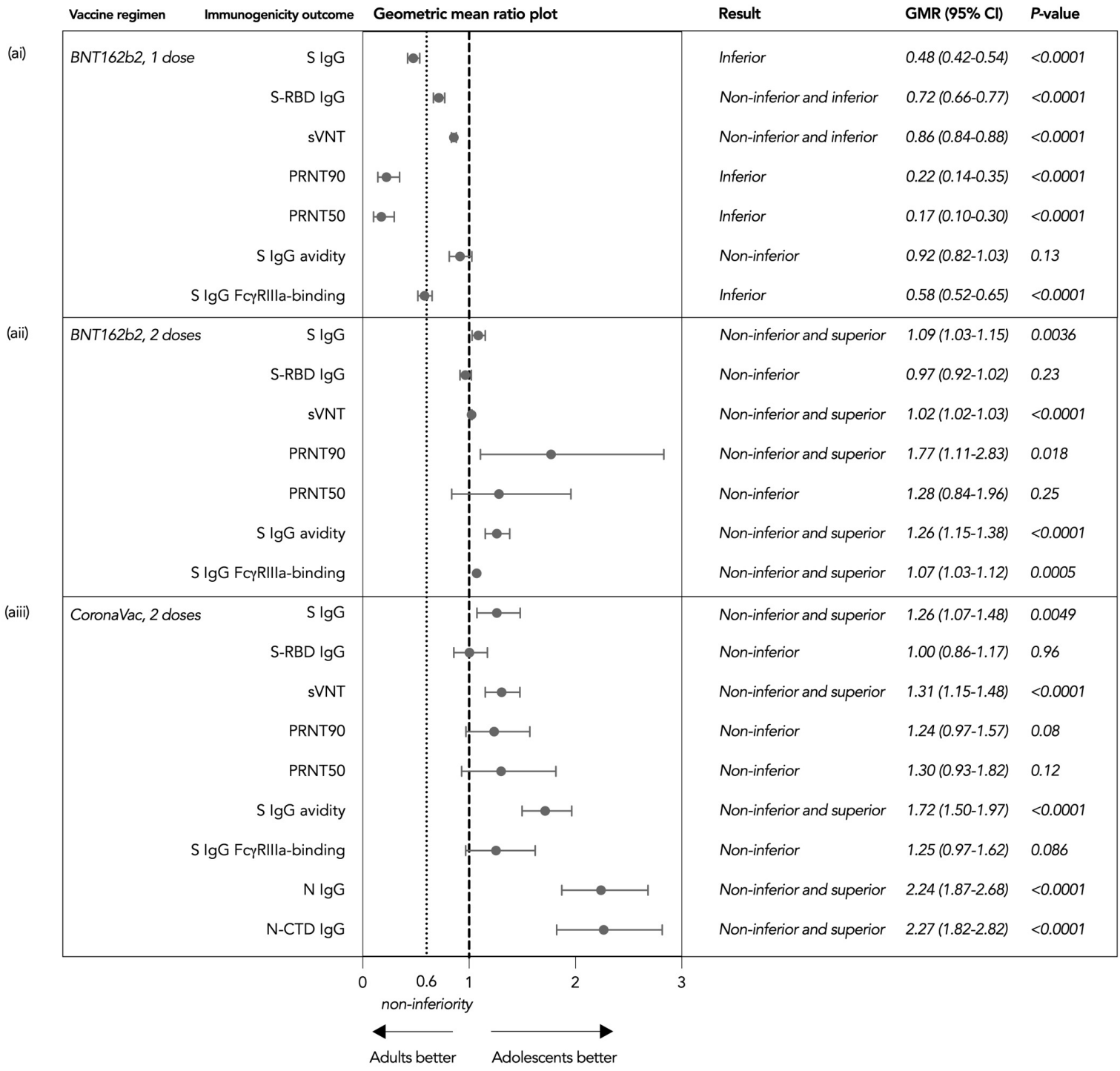

Vaccine regimen
Immunogenicity outcome
Geometric mean ratio plot
Result
GMR (95% CI)
P-value
(ai)
BNT162b2, 1 dose
S IgG
Inferior
0.48 (0.42-0.54)
<0.0001
S-RBD IgG
Non-inferior and inferior
0.72 (0.66-0.77)
<0.0001
sVNT
Non-inferior and inferior
0.86 (0.84-0.88)
<0.0001
PRNT90
Inferior
0.22 (0.14-0.35)
<0.0001
PRNT50
Inferior
0.17 (0.10-0.30)
<0.0001
S IgG avidity
Non-inferior
0.92 (0.82-1.03)
0.13
S IgG FcγRIIIa-binding
Inferior
0.58 (0.52-0.65)
<0.0001
(aii)
BNT162b2, 2 doses
S IgG
Non-inferior and superior
1.09 (1.03-1.15)
0.0036
S-RBD IgG
Non-inferior
0.97 (0.92-1.02)
0.23
sVNT
Non-inferior and superior
1.02 (1.02-1.03)
<0.0001
PRNT90
Non-inferior and superior
1.77 (1.11-2.83)
0.018
PRNT50
Non-inferior
1.28 (0.84-1.96)
0.25
S IgG avidity
Non-inferior and superior
1.26 (1.15-1.38)
<0.0001
S IgG FcγRIIIa-binding
Non-inferior and superior
1.07 (1.03-1.12)
0.0005
(aiii)
CoronaVac, 2 doses
S IgG
Non-inferior and superior
1.26 (1.07-1.48)
0.0049
S-RBD IgG
Non-inferior
1.00 (0.86-1.17)
0.96
sVNT
Non-inferior and superior
1.31 (1.15-1.48)
<0.0001
PRNT90
Non-inferior
1.24 (0.97-1.57)
0.08
PRNT50
Non-inferior
1.30 (0.93-1.82)
0.12
S IgG avidity
Non-inferior and superior
1.72 (1.50-1.97)
<0.0001
S IgG FcγRIIIa-binding
Non-inferior
1.25 (0.97-1.62)
0.086
N IgG
Non-inferior and superior
2.24 (1.87-2.68)
<0.0001
N-CTD IgG
Non-inferior and superior
2.27 (1.82-2.82)
<0.0001
0
0.6
1
2
3
non-inferiority
Adults better
Adolescents better

Fig. 1b

	Vaccine regimen	Immunogenicity outcome	Geometric mean ratio plot	Result	GMR (95% CI)	*P*-value
(bi)	*BNT162b2, 1 dose*	S-specific IFN-γ$^+$CD4$^+$ T cells		*Inconclusive*	*0.42 (0.22-1.23)*	*0.01*
		S-specific IL-2$^+$ CD4$^+$ T cells		*Inconclusive*	*0.81 (0.46-1.45)*	*0.48*
		S-specific IFN-γ$^+$ CD8$^+$ T cells		*Inconclusive*	*0.69 (0.34-1.38)*	*0.29*
		S-specific IL-2$^+$ CD8$^+$ T cells		*Inconclusive*	*0.74 (0.50-1.10)*	*0.21*
(bii)	*BNT162b2, 2 doses*	S-specific IFN-γ$^+$CD4$^+$ T cells		*Non-inferior*	*1.23 (0.66-2.29)*	*0.51*
		S-specific IL-2$^+$ CD4$^+$ T cells		*Non-inferior*	*1.15 (0.67-1.99)*	*0.60*
		S-specific IFN-γ$^+$ CD8$^+$ T cells		*Non-inferior*	*1.32 (0.64-2.73)*	*0.44*
		S-specific IL-2$^+$ CD8$^+$ T cells		*Inconclusive*	*0.78 (0.51-1.21)*	*0.26*
(biii)	*CoronaVac, 2 doses*	SNM-specific IFN-γ$^+$CD4$^+$ T cells		*Inconclusive*	*0.85 (0.47-1.55)*	*0.60*
		SNM-specific IL-2$^+$ CD4$^+$ T cells		*Non-inferior*	*0.99 (0.64-1.55)*	*0.98*
		SNM-specific IFN-γ$^+$ CD8$^+$ T cells		*Non-inferior*	*1.23 (0.62-2.46)*	*0.55*
		SNM-specific IL-2$^+$ CD8$^+$ T cells		*Non-inferior*	*0.88 (0.61-1.28)*	*0.50*
		S-specific IFN-γ$^+$CD4$^+$ T cells		*Inconclusive*	*1.13 (0.53-2.40)*	*0.74*
		S-specific IL-2$^+$ CD4$^+$ T cells		*Inconclusive*	*0.97 (0.56-1.68)*	*0.92*
		S-specific IFN-γ$^+$ CD8$^+$ T cells		*Inconclusive*	*0.98 (0.43-2.25)*	*0.96*
		S-specific IL-2$^+$ CD8$^+$ T cells		*Inconclusive*	*0.93 (0.58-1.50)*	*0.78*
		N-specific IFN-γ$^+$CD4$^+$ T cells		*Non-inferior*	*1.17 (0.61-2.23)*	*0.64*
		N-specific IL-2$^+$ CD4$^+$ T cells		*Non-inferior*	*1.09 (0.64-1.85)*	*0.76*
		N-specific IFN-γ$^+$ CD8$^+$ T cells		*Non-inferior*	*1.33 (0.65-2.70)*	*0.43*
		N-specific IL-2$^+$ CD8$^+$ T cells		*Non-inferior*	*1.02 (0.69-1.50)*	*0.92*
		M-specific IFN-γ$^+$CD4$^+$ T cells		*Inconclusive*	*0.79 (0.41-1.52)*	*0.48*
		M-specific IL-2$^+$ CD4$^+$ T cells		*Inconclusive*	*0.90 (0.59-1.38)*	*0.63*
		M-specific IFN-γ$^+$ CD8$^+$ T cells		*Non-inferior*	*1.25 (0.66-2.35)*	*0.49*
		M-specific IL-2$^+$ CD8$^+$ T cells		*Non-inferior*	*0.95 (0.66-1.37)*	*0.79*

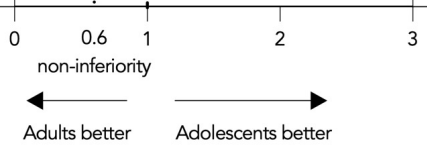


Fig. 1 | Immunogenicity outcomes for adolescents were mostly non-inferior in adolescents in comparison to adults. **ai**, One dose of BNT162b2 (B) in adolescents was non-inferior by S-RBD IgG, sVNT and S IgG avidity but not by S IgG, PRNT90, PRNT50 and S IgG FcγRIIIa-binding (all $P<0.0001$, except S IgG avidity with $P=0.13$), which failed the non-inferiority comparison to adults. Additionally, although non-inferiority was satisfied for S-RBD IgG and sVNT for B in adolescents, their CIs were also within the inferior ranges (both $P<0.0001$). **aii**, In contrast, humoral responses in adolescents were non-inferior to adults after 2 doses of BNT162b2 (BB), as measured by S IgG (also superior, $P=0.0036$), S-RBD IgG ($P=0.23$), sVNT (also superior, $P<0.0001$), PRNT90 (also superior, $P=0.018$), PRNT50 ($P=0.25$), S IgG avidity (also superior, $P<0.0001$) and S IgG FcγRIIIa-binding (also superior, $P=0.0005$). **aiii**, After 2 doses of CoronaVac (CC), adolescents also had non-inferior humoral responses to adults as assessed by S IgG (also superior, $P=0.0049$), S-RBD IgG ($P=0.96$), sVNT (also superior, $P<0.0001$), PRNT90 ($P=0.08$), PRNT50 ($P=0.12$), S IgG avidity (also superior, $P<0.0001$) and S IgG FcγRIIIa-binding ($P=0.086$). Additionally for adolescent CC, N and N-CTD IgGs were non-inferior and superior for adolescents compared to adults (both $P<0.0001$). **bi-ii**, Fifty-eight B, 56 BB and **biii**, 60 adolescent CC were tested for IFN-γ^+ and IL-2^+ $CD4^+$ and $CD8^+$ T cells on flow-cytometry-based intracellular cytokine staining assays specific to S (and N and M for CC) for 21 days after dose 1 and 28 days after dose 2. The results of SNM-specific T cell responses were calculated from the sum of responses of the individual S, N and M peptide pools. S-specific IFN-γ^+CD4^+, IL-2^+CD4^+ and IFN-γ^+CD8^+ T cell responses were non-inferior for adolescent BB in comparison to adults. For adolescent CC compared to adults, SNM-specific IL-2^+CD4^+, IFN-γ^+CD8^+ and IL-2^+CD8^+, N-specific IFN-γ^+CD4^+, IL-2^+CD4^+, IFN-γ^+CD8^+ and IL-2^+CD8^+, M-specific IFN-γ^+CD8^+ and IL-2^+CD8^+ were non-inferior. The remaining cellular immunogenicity outcomes were inconclusive. Dots and error bars show GMR estimates and 95% CI respectively. GMR, geometric mean ratio; CI, confidence interval; S, spike protein; RBD, receptor-binding domain; N, nucleocapsid protein; M, membrane protein; sVNT, surrogate virus neutralization test; PRNT, plaque reduction neutralization test; FcγRIIIa, Fcγ receptor IIIa; IFN-γ, interferon-γ; IL-2, interleukin-2.

Fig. 2

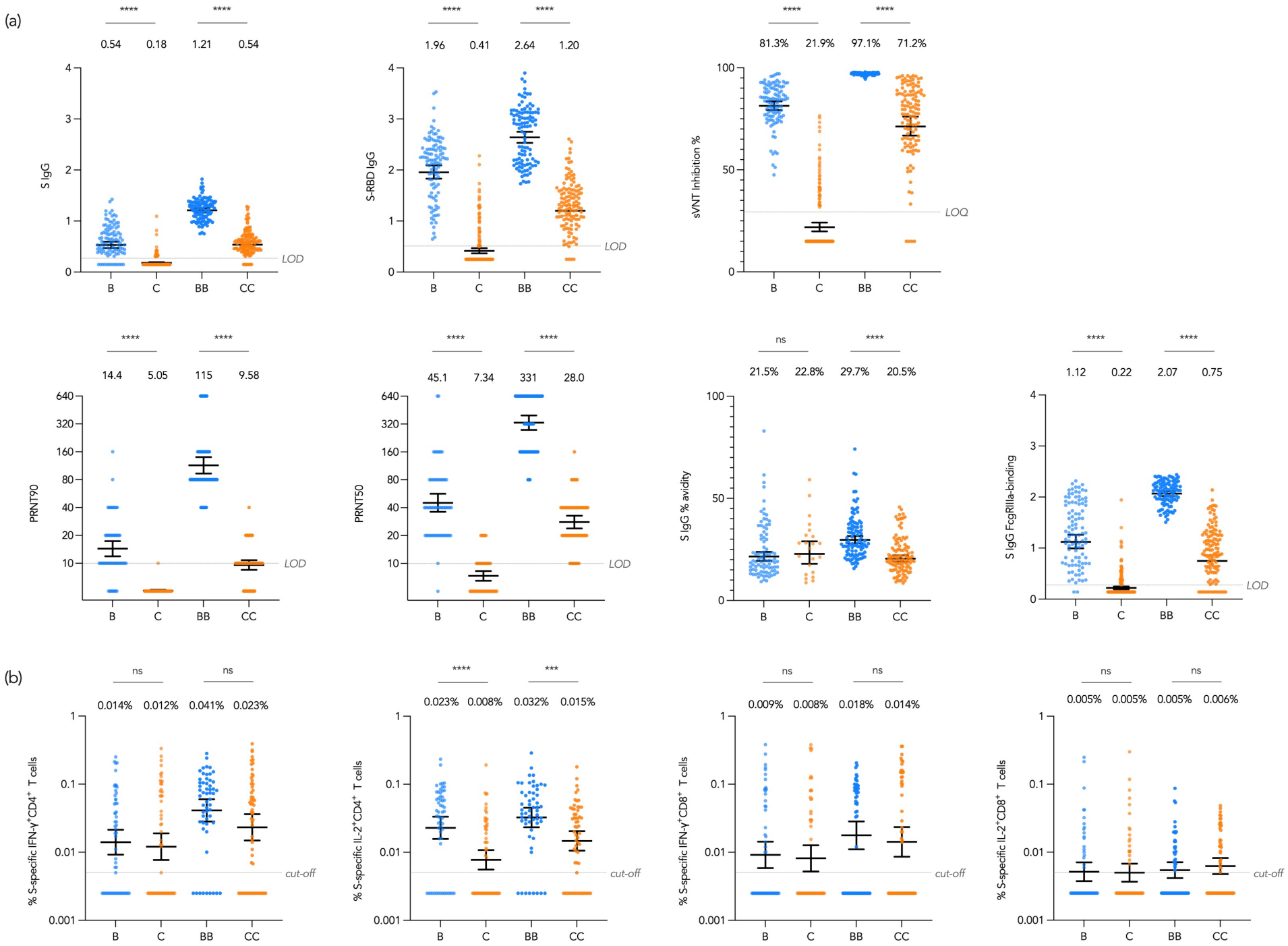

(a)
S IgG
0.54 0.18 1.21 0.54
LOD
S-RBD IgG
1.96 0.41 2.64 1.20
LOD
sVNT Inhibition %
81.3% 21.9% 97.1% 71.2%
LOQ
PRNT90
14.4 5.05 115 9.58
LOD
PRNT50
45.1 7.34 331 28.0
LOD
S IgG % avidity
ns ****
21.5% 22.8% 29.7% 20.5%
S IgG FcgRIIIa-binding
1.12 0.22 2.07 0.75
LOD
(b)
% S-specific IFN-γ+CD4+ T cells
ns ns
0.014% 0.012% 0.041% 0.023%
cut-off
% S-specific IL-2+CD4+ T cells
**** ***
0.023% 0.008% 0.032% 0.015%
cut-off
% S-specific IFN-γ+CD8+ T cells
ns ns
0.009% 0.008% 0.018% 0.014%
cut-off
% S-specific IL-2+CD8+ T cells
ns ns
0.005% 0.005% 0.005% 0.006%
cut-off
B C BB CC

Fig. 2 | Antibody levels against S were higher for BNT162b2 than CoronaVac in adolescents. Humoral and cellular immunogenicity was compared between vaccines in adolescents at 21-28 days after 1 dose and 28 days after 2 doses. **a**, There were lower humoral responses after CC than BB as measured by S IgG (GM OD450 0.54 vs 1.21; GMR 0.44, 95% CI 0.40-0.49), S-RBD IgG (GM OD450 1.20 vs 2.64; GMR 0.46, 95% CI 0.41-0.50), sVNT (GM % inhibition 71.2% vs 97.1%; GMR 0.73, 95% CI 0.68-0.79), PRNT90 (GM PRNT90 9.58 vs 115; GMR 0.08, 95% CI 0.07-0.11), PRNT50 (GM PRNT50 28.0 vs 331; GMR 0.08, 95% CI 0.07-0.11), S IgG avidity index (GM % avidity 20.5% vs 29.7%; GMR 0.69, 95% CI 0.63-0.76) and S IgG FcγRIIIa-binding (GM OD450 0.75 vs 2.07; GMR 0.36, 95% CI 0.31-0.42) (all P<0.0001). Most outcomes except S IgG avidity were also lower in C compared to B. **b**, Cellular immunogenicity outcomes were similar between vaccine types except for the S-specific IL-2$^+$CD4$^+$ T cell response, which was lower after CC (GM % T cells 0.015% vs 0.032%; GMR 0.45, 95% CI 0.28-0.72) (P=0.001). Nucleocapsid (N) and membrane (M)-specific T cell responses were not compared since only CC but not BB had induced non-spike responses, as expected. Data labels and centre lines show GM estimates, and error bars show 95% CI. GM, geometric mean; GMR, geometric mean ratio; CI, confidence interval; B, 1 dose of BNT162b2; BB, 2 doses of BNT162b2; C, 1 dose of CoronaVac; CC, 2 doses of CoronaVac; S, spike protein; RBD, receptor-binding domain; sVNT, surrogate virus neutralization test; PRNT, plaque reduction neutralization test; FcγRIIIa, Fcγ receptor IIIa; IFN-γ, interferon-γ; IL-2, interleukin-2. ***, P<0.001; ****, P<0.0001.

Fig. 3

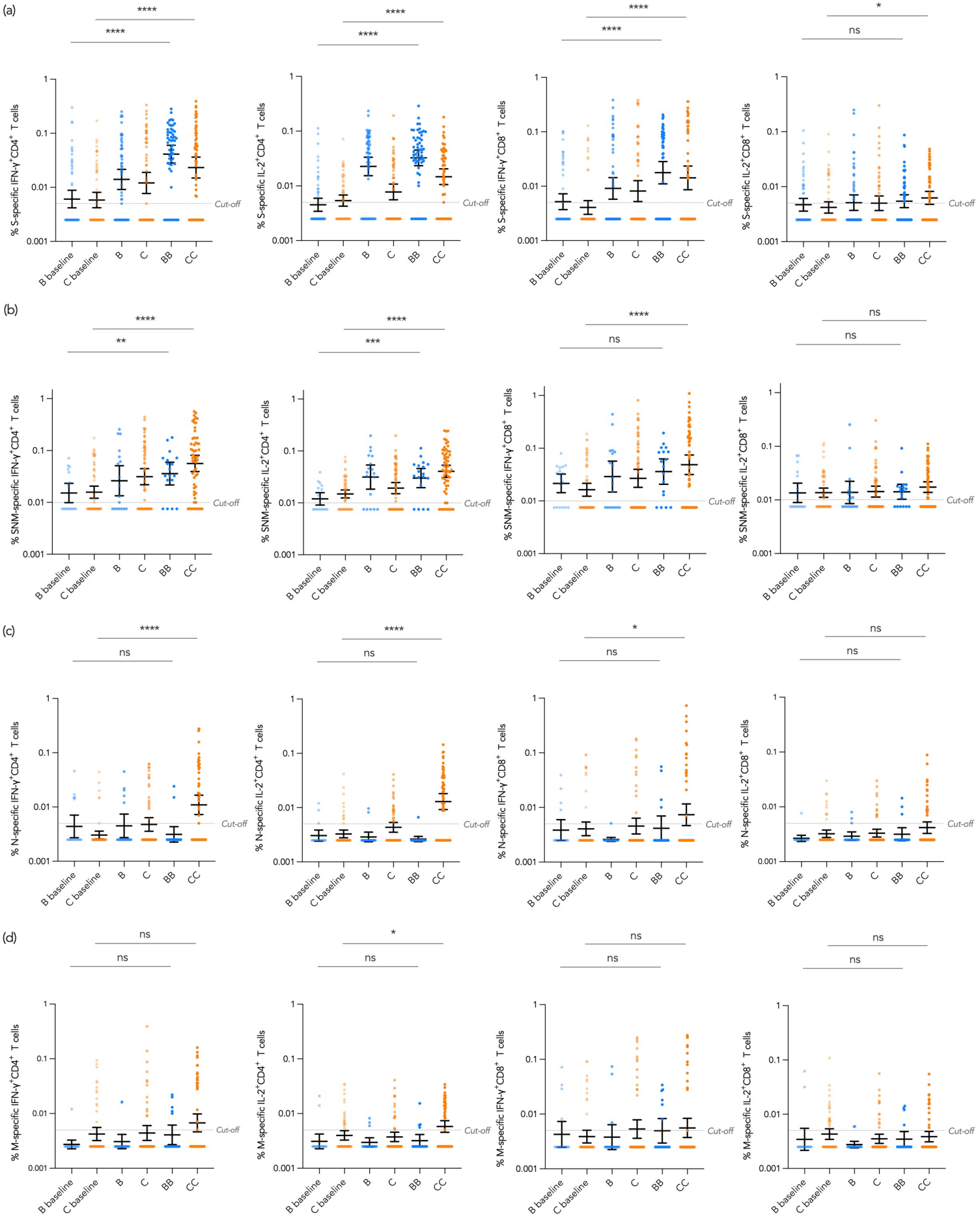

(a)
(b)
(c)
(d)
% S-specific IFN-γ+CD4+ T cells
% S-specific IL-2+CD4+ T cells
% S-specific IFN-γ+CD8+ T cells
% S-specific IL-2+CD8+ T cells
% SNM-specific IFN-γ+CD4+ T cells
% SNM-specific IL-2+CD4+ T cells
% SNM-specific IFN-γ+CD8+ T cells
% SNM-specific IL-2+CD8+ T cells
% N-specific IFN-γ+CD4+ T cells
% N-specific IL-2+CD4+ T cells
% N-specific IFN-γ+CD8+ T cells
% N-specific IL-2+CD8+ T cells
% M-specific IFN-γ+CD4+ T cells
% M-specific IL-2+CD4+ T cells
% M-specific IFN-γ+CD8+ T cells
% M-specific IL-2+CD8+ T cells
1
0.1
0.01
0.001
Cut-off
B baseline
C baseline
B
C
BB
CC
****
**
***
*
ns

Fig. 3 | Significant increases in N- and M-specific T cell responses after CoronaVac in adolescents. **a**, For adolescents who received each vaccine, when compared to their own baseline values, BB and CC had significant increases in T cell responses for S-specific IFN-γ^+CD4$^+$, IL-2$^+$CD4$^+$ and IFN-γ^+CD8$^+$ (all P<0.0001). Additionally, a significant increase in S-specific IL-2$^+$CD8$^+$ T cells was observed for CC (P=0.023). **b**, When added together, SNM-specific IFN-γ^+CD4$^+$ (P<0.0001), IL-2$^+$CD4$^+$ (P<0.0001) and IFN-γ^+CD8$^+$ T cells (P<0.0001) increased significantly for CC. **c**, These marked increases were likely due to post-CC's combined increases in S-specific T cell responses as well as N-specific increases in IFN-γ^+CD4$^+$ (P<0.0001), IL-2$^+$CD4$^+$ (P<0.0001), IFN-γ^+CD8$^+$ (P=0.042) and **d**, M-specific IL-2$^+$CD4$^+$ (P=0.021). On the other hand, no significant N- and M-specific T cell responses were elicited by BB, an expected result. Centre lines show GM estimates, and error bars show 95% CI. GM, geometric mean; CI, confidence interval; B, 1 dose of BNT162b2; BB, 2 doses of BNT162b2; C, 1 dose of CoronaVac; CC, 2 doses of CoronaVac; S, spike protein; N, nucleocapsid protein; M, membrane protein; IFN-γ, interferon-γ; IL-2, interleukin-2. *, P<0.05; ***, P<0.001; ****, P<0.0001.

Fig. 4

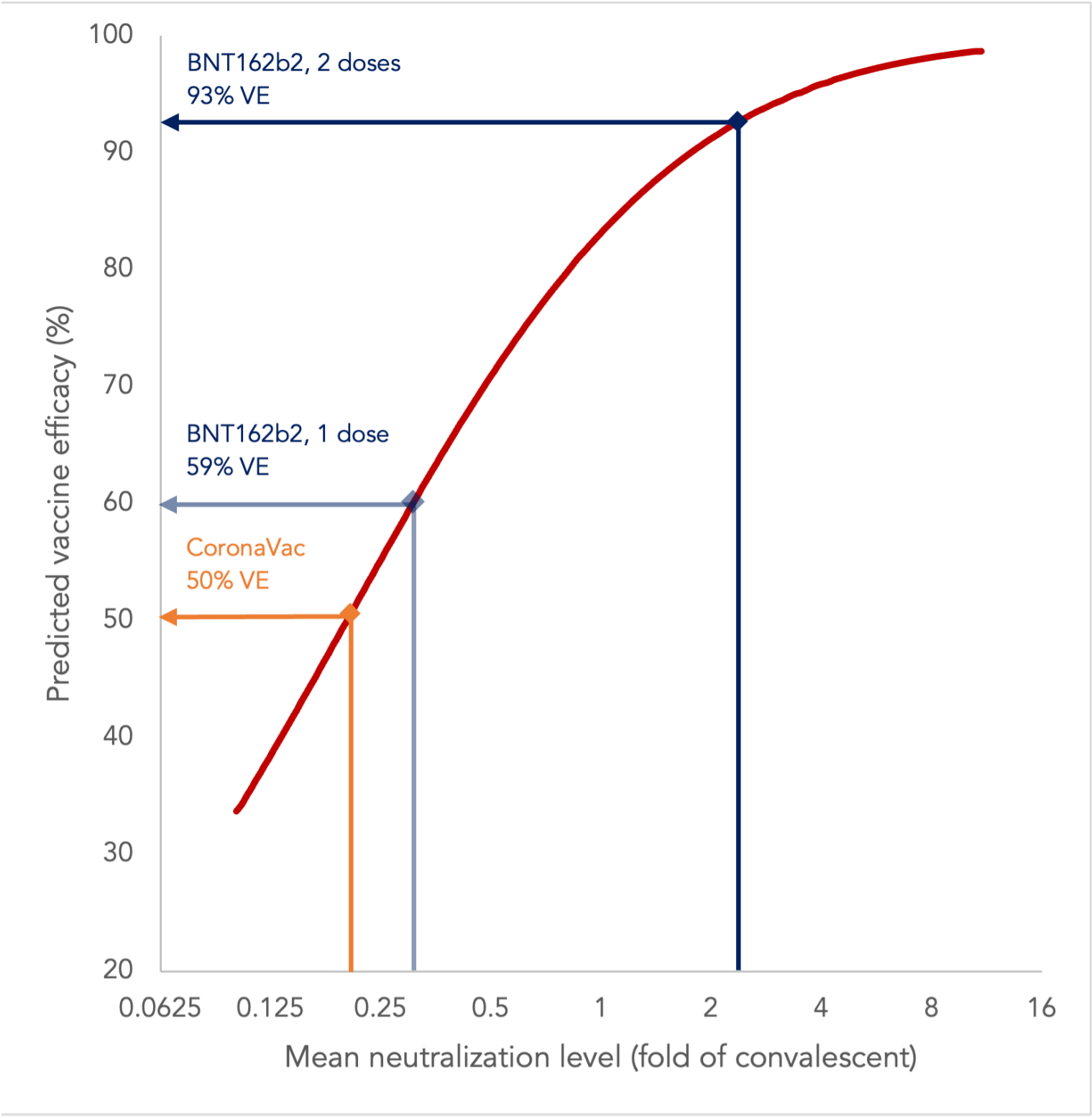

100
90
80
70
60
50
40
30
20
Predicted vaccine efficacy (%)
BNT162b2, 2 doses
93% VE
BNT162b2, 1 dose
59% VE
CoronaVac
50% VE
0.0625
0.125
0.25
0.5
1
2
4
8
16
Mean neutralization level (fold of convalescent)

Fig. 4 | Vaccine efficacy estimates based on neutralizing antibody titres for BNT162b2 (after 1 dose or 2 doses) and CoronaVac (after 2 doses) were ≥50% in adolescents. Neutralizing antibodies have been established as a reliable correlate of protection that can predict VEs against symptomatic COVID-19. The mean neutralizing levels (fold of convalescent) were derived by dividing the geometric mean titres of PRNT90 in healthy evaluable adolescents who received the vaccines with that of 102 convalescent sera collected on days 28-59 post-onset of illness in patients aged ≥18 years. A point estimate of VE was extrapolated from the best fit of the logistic model in Khoury et al.[12,38,39] Adolescent B has been considered completion of primary series, but not adolescent CC or adult B, for a time period in HK and the UK due to elevated myocarditis risks after youths received 2 doses of BNT162b2. Therefore, the VE of adolescent B, but not adolescent C or adult CC, was also extrapolated, along with adolescent BB and CC. The mean neutralization levels (fold of convalescent) for adolescents after receiving 2 doses of BNT162b2, 2 doses of CoronaVac and 1 dose of BNT162b2 were 2.39, 0.20 and 0.30, respectively. Extrapolation of these mean neutralization levels using the logistic model resulted in VEs of 93% after 2 doses of BNT162b2, 50% after 2 doses of CoronaVac and 59% after 1 dose of BNT162b2. VE, vaccine efficacy.

Fig. 5

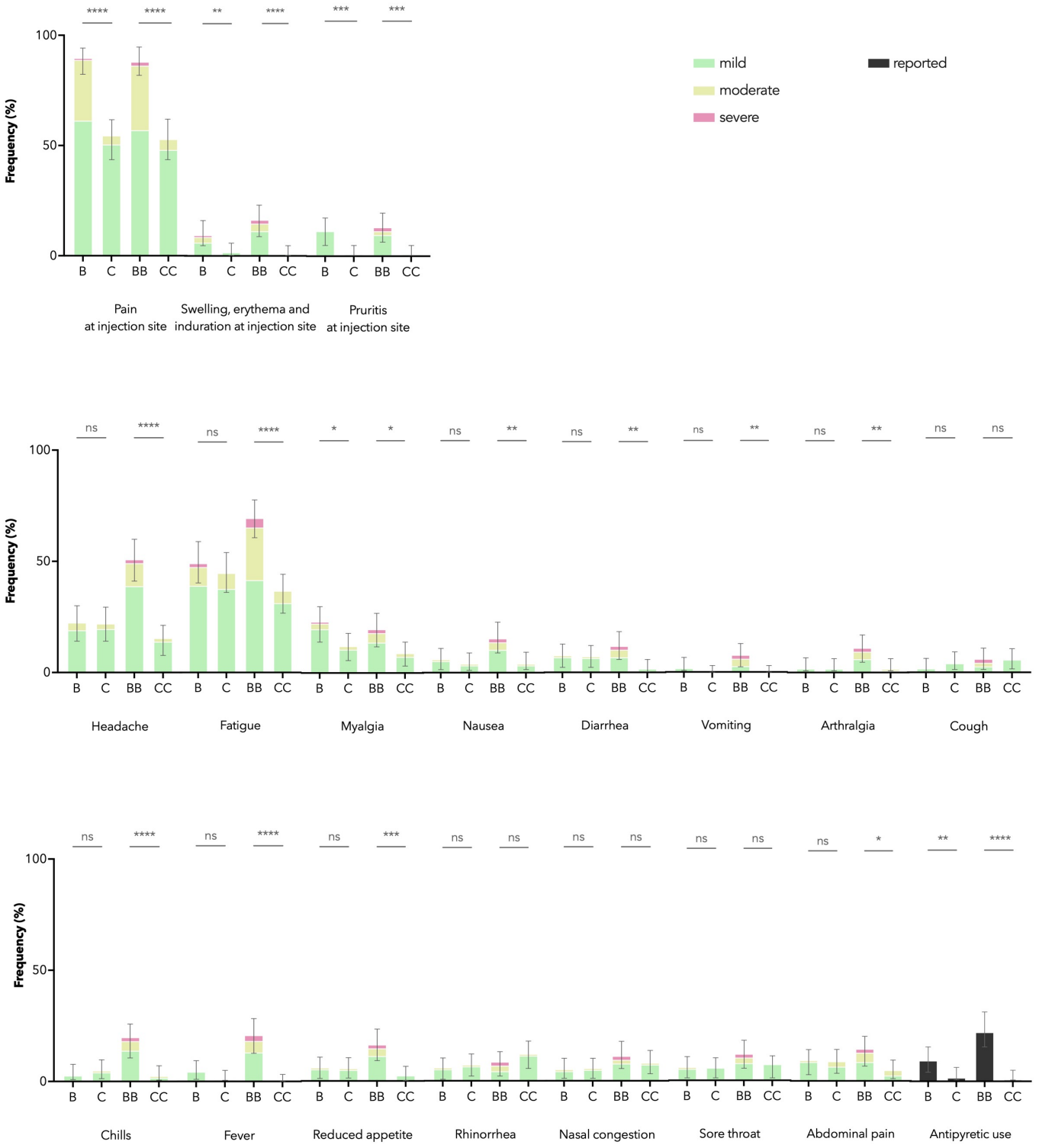

mild
moderate
severe
reported
Frequency (%)
100
50
0
B C BB CC
Pain at injection site
Swelling, erythema and induration at injection site
Pruritis at injection site
Headache
Fatigue
Myalgia
Nausea
Diarrhea
Vomiting
Arthralgia
Cough
Chills
Fever
Reduced appetite
Rhinorrhea
Nasal congestion
Sore throat
Abdominal pain
Antipyretic use

Fig. 5 | Adverse reactions 7 days after each dose of BNT162b2 and CoronaVac were solicited from adolescents in the healthy safety population. In the adolescent healthy safety population, pain at the injection site was the most common adverse reaction (ARs) reported for both vaccines, which was significantly more for those who received BNT162b2 (*N*=116) than CoronaVac (*N*=123) (B: 89.7% vs C: 54.5%, *P*<0.0001; BB: 87.9% vs CC: 52.9%, *P*<0.0001). BNT162b2 was also associated with more reporting of several other ARs, including swelling, erythema, induration and pruritis at the injection site, headache, fatigue, myalgia, nausea, diarrhoea, vomiting, arthralgia, chills, fever, reduced appetite and abdominal pain. More participants had antipyretics use after either dose of BNT162b2 than CoronaVac (B: 9.5% vs C: 1.6%, *P*=0.009; BB: 22.4% vs CC: 0.8%, *P*<0.0001). Error bars show 95% CI of the total frequency of the respective AR of any severity. CI, confidence interval; B, 1 dose of BNT162b2; BB, 2 doses of BNT162b2; C, 1 dose of CoronaVac; CC, 2 doses of CoronaVac. *, *P*<0.05; **, *P*<0.01; ***, *P*<0.001; ****, *P*<0.0001.

EXTENDED DATA TABLES

Extended Data Table 1. Participant disposition in healthy safety population.			
	BNT162b2	**CoronaVac**	**Total**
Healthy adolescents			
Participants	116	123	239
Male sex	71 (61.2%)	66 (53.7%)	137 (57.3%)
Han Chinese	97 (83.6%)	123 (100.0%)	220 (92.1%)
Age (years)	13.7 (1.5)	14.2 (1.9)	14.0 (1.7)
Healthy adults			
Participants	147	141	288
Male sex	68 (46.3%)	54 (38.3%)	122 (42.4%)
Han Chinese	133 (90.5%)	141 (100%)	274 (95.1%)
Age (years)	47.5 (8.5)	47.5 (6.4)	47.5 (7.5)
Values are either counts, (percentages%) or means (standard deviations).			

Extended Data Table 2. Humoral immunogenicity outcomes and non-inferiority hypothesis testing in expanded immunogenicity populations by vaccine regimen.

	BNT162b2			CoronaVac	
	Adolescents 1 dose	Adolescents 2 doses	Adults 2 doses	Adolescents 2 doses	Adults 2 doses
Antibody response					
S IgG on ELISA					
N	109	105	139	117	83
GM OD450 value (95% CI)	0.54 (0.49-0.61)	1.21 (1.17-1.25)	1.11 (1.07-1.16)	0.54 (0.49-0.58)	0.39 (0.34-0.44)
% positive (>/=LOD at 0.3)	88.1% *P*=0.0001	100% *P*>0.9999	99.3%	94.0% *P*=0.0006	77.1%
GMR (95% CI)	0.49 (0.44-0.55) Not non-inferior *P*<0.0001	1.09 (1.03-1.15) Non-inferior *P*=0.0022	/	1.37 (1.19-1.58) Non-inferior *P*<0.0001	/
S-RBD IgG on ELISA					
N	116	106	139	120	84
GM OD450 value (95% CI)	1.94 (1.82-2.06)	2.64 (2.54-2.75)	2.79 (2.70-2.89)	1.20 (1.10-1.31)	1.14 (1.01-1.30)
% positive (>/=LOD at 0.5)	100% *P*>0.9999	100% *P*>0.9999	100%	96.7% *P*= 0.21	91.7%
GMR (95% CI)	0.69 (0.65-0.74) Non-inferior *P*<0.0001	0.95 (0.90-1.00) Non-inferior *P*= 0.035	/	1.05 (0.91-1.21) Non-inferior *P*= 0.52	/
S-RBD ACE2-blocking antibody on sVNT					
N	116	106	139	120	84
GM % inhibition (95% CI)	80.6% (78.2-83.0%)	97.1% (97.0-97.2%)	94.9% (94.4-95.4%)	70.9% (66.5-75.7%)	48.3% (43.1-54.1%)
% positive (>/=LOQ at 30%)	100% *P*>0.9999	100% *P*>0.9999	100%	96.7% *P*= 0.01	86.9%
GMR (95% CI)	0.85 (0.83-0.87) Non-inferior *P*<0.0001	1.02 (1.02-1.03) Non-inferior *P*<0.0001	/	1.47 (1.30-1.66) Non-inferior *P*<0.0001	/
Neutralizing antibody on PRNT					
N	64	60	13	64	19
GM PRNT90 (95% CI)	14.5 (12.0-17.4)	115 (93.3-140)	64.6 (43.5-96.1)	9.58 (8.50-10.8)	7.75 (6.35-9.46)
% positive (>/=LOD at 10)	85.9% *P*= 0.34	100% *P*>0.9999	100%	75.0% *P*= 0.16	57.9%
GMR (95% CI)	0.22 (0.14-0.35) Not non-inferior *P*<0.0001	1.77 (1.11-2.83) Non-inferior *P*= 0.018	/	1.24 (0.97-1.57) Non-inferior *P*= 0.08	/
GM PRNT50 (95% CI)	45.6 (36.5-56.9)	331 (277-396)	259 (168-398)	28.0 (23.9-32.8)	21.5 (15.4-30.0)
% positive (>/=LOD at 10)	98.4% *P*>0.9999	100% *P*>0.9999	100%	100% *P*= 0.23	94.7%
GMR (95% CI)	0.18 (0.10-0.30) Not non-inferior *P*<0.0001	1.28 (0.84-1.96) Non-inferior *P*= 0.25	/	1.30 (0.93-1.82) Non-inferior *P*= 0.12	/
S IgG avidity on ELISA					
N	96	105	138	110	64
GM avidity index (95% CI)	21.4% (19.5-23.5)	29.8% (28.0-31.6)	23.6% (22.1-25.1)	20.5% (19.1-22.1)	13.1% (11.9-14.4)
GMR (95% CI)	0.91 (0.82-1.01) Non-inferior *P*=0.08	1.26 (1.16-1.38) Non-inferior *P*<0.0001	/	1.57 (1.39-1.77) Non-inferior *P*<0.0001	/
S IgG FcγRIIIa-binding on ELISA					
N	109	105	139	117	83
GM OD450 value (95% CI)	1.13 (1.01-1.28)	2.07 (2.02-2.12)	1.93 (1.88-1.98)	0.75 (0.65-0.86)	0.54 (0.46-0.65)
% positive (>/=LOD at 0.28)	97.3% *P*=0.08	100% *P*>0.9999	100%	87.2% *P*=0.24	80.7%
GMR (95% CI)	0.59 (0.53-0.66) Not non-inferior *P*<0.0001	1.07 (1.03-1.11) Non-inferior *P*=0.0003	/	1.37 (1.10-1.72) Non-inferior *P*=0.005	/
N IgG on ELISA					

N	/	/	/	64	21
GM OD450 value (95% CI)	/	/	/	1.72 (1.61-1.83)	0.77 (0.59-0.99)
% positive (>/=LOD at 0.88)	/	/	/	98.4% *P*<0.0001	52.4%
GMR (95% CI)	/	/	/	2.24 (1.87-2.68) Non-inferior *P*<0.0001	/
N-CTD IgG on ELISA					
N	/	/	/	64	21
GM OD450 value (95% CI)	/	/	/	2.09 (1.89-2.31)	0.92 (0.73-1.17)
% positive (>/=LOD at 1.34)	/	/	/	92.2% *P*<0.0001	28.6%
GMR (95% CI)	/	/	/	2.27 (1.82-2.82) Non-inferior *P*<0.0001	/

GM, geometric mean; GMR, geometric mean ratio; OD, optical density; CI, confidence interval; LOD, limit of detection; LOQ, limit of quantification; PRNT90, 90% plaque reduction neutralization titre; PRNT50, 50% plaque reduction neutralization titre; FcγRIIIa: Fc gamma receptor III-a; S, spike protein; RBD, receptor-binding domain; ELISA, enzyme-linked immunosorbent assay; ACE-2, angiotensin-converting enzyme-2; sVNT, surrogate virus neutralization test; PRNT, plaque reduction neutralization test; N, nucleocapsid protein; CTD, C-terminal domain.

Extended Data Table 3. Cellular immunogenicity outcomes and non-inferiority hypothesis testing in expanded immunogenicity populations by vaccine regimen.

	BNT162b2			**CoronaVac**	
	Adolescents 1 dose	**Adolescents 2 doses**	**Adults 2 doses**	**Adolescents 2 doses**	**Adults 2 doses**
T cell responses					
S-specific T cell responses on flow cytometry					
N	59	56	47	60	36
GM % IFN-γ^+CD4$^+$ T cells (95% CI)	0.015% (0.010-0.023%)	0.041% (0.028-0.060%)	0.033% (0.020-0.056%)	0.023% (0.015-0.036%)	0.021% (0.011-0.039%)
% positive (>= cut-off at 0.005%)	62.7% *P*= 0.22	83.9% *P*= 0.33	74.5%	70.0% *P*= 0.38	61.1%
GMR (95% CI)	0.45 (0.23-0.87) Not non-inferior *P*= 0.02	1.23 (0.66-2.29) Non-inferior *P*= 0.51	/	1.13 (0.53-2.40) Inconclusive *P*= 0.74	/
GM % IL-2$^+$ CD4$^+$ T cells (95% CI)	0.023% (0.016-0.034%)	0.032% (0.023-0.045%)	0.028% (0.018-0.044%)	0.015% (0.011-0.020%)	0.015% (0.010-0.024%)
% positive (>= cut-off at 0.005%)	74.6% *P*> 0.9999	85.7% *P*= 0.31	76.6%	73.3% *P*= 0.82	69.4%
GMR (95% CI)	0.83 (0.47-1.47) Inconclusive *P*= 0.52	1.15 (0.67-1.99) Non-inferior *P*= 0.60	/	0.97 (0.56-1.68) Inconclusive *P*= 0.92	/
GM % IFN-γ^+CD8$^+$ T cells (95% CI)	0.009% (0.006-0.014%)	0.018% (0.011-0.028%)	0.013% (0.008-0.024%)	0.014% (0.009-0.023%)	0.015% (0.007-0.029%)
% positive (>= cut-off at 0.005%)	40.7% *P*= 0.56	57.1% *P*= 0.33	46.8%	48.3% *P*= 0.83	44.4%
GMR (95% CI)	0.67 (0.33-1.35) Inconclusive *P*= 0.26	1.32 (0.64-2.73) Non-inferior *P*= 0.44	/	0.98 (0.43-2.25) Inconclusive *P*= 0.96	/
GM % IL-2$^+$ CD8$^+$ T cells (95% CI)	0.005% (0.004-0.007%)	0.005% (0.004-0.007%)	0.007% (0.005-0.010%)	0.006% (0.005-0.008%)	0.007% (0.004-0.010%)
% positive (>= cut-off at 0.005%)	32.2% *P*= 0.11	44.6% *P*= 0.70	48.9%	48.3% *P*= 0.67	41.7%
GMR (95% CI)	0.73 (0.49-1.09) Inconclusive *P*= 0.19	0.78 (0.51-1.21) Inconclusive *P*= 0.26	/	0.93 (0.58-1.50) Inconclusive *P*= 0.78	/
Total S, N and M-specific T cell responses on flow cytometry					
N	/	/	/	60	36
GM % IFN-γ^+CD4$^+$ T cells (95% CI)	/	/	/	0.058% (0.041-0.083%)	0.068% (0.041-0.113%)
% positive (>= cut-off at 0.01%)	/	/	/	83.3% *P*= 0.59	77.8%
GMR (95% CI)	/	/	/	0.85 (0.47-1.55) Inconclusive *P*= 0.60	/
GM % IL-2$^+$CD4$^+$ T cells (95% CI)	/	/	/	0.039% (0.030-0.052%)	0.040% (0.027-0.057%)
% positive (>= cut-off at 0.01%)	/	/	/	83.3% *P*= 0.59	77.8%
GMR (95% CI)	/	/	/	0.99 (0.64-1.55) Non-inferior *P*= 0.98	/
GM % IFN-γ^+CD8$^+$ T cells (95% CI)	/	/	/	0.050% (0.033-0.077%)	0.041% (0.023-0.071%)
% positive (>= cut-off at 0.01%)	/	/	/	65.0% *P*= 0.52	58.3%
GMR (95% CI)	/	/	/	1.23 (0.62-2.46) Non-inferior *P*= 0.55	/
GM % IL-2$^+$CD8$^+$ T cells (95% CI)	/	/	/	0.017% (0.014-0.022%)	0.020% (0.014-0.027%)
% positive (>= cut-off at 0.01%)	/	/	/	58.3% *P*>0.9999	58.3%
GMR (95% CI)	/	/	/	0.88 (0.61-1.28) Non-inferior *P*= 0.50	/

N-specific T cell responses on flow cytometry					
N	/	/	/	60	36
GM % IFN-γ$^+$CD4$^+$ T cells (95% CI)	/	/	/	0.011% (0.008-0.017%)	0.010% (0.006-0.016%)
% positive (>= cut-off at 0.005%)	/	/	/	55.0% *P*= 0.68	50.0%
GMR (95% CI)	/	/	/	1.17 (0.61-2.23) Non-inferior *P*= 0.64	/
GM % IL-2$^+$CD4$^+$ T cells (95% CI)	/	/	/	0.013% (0.009-0.018%)	0.012% (0.008-0.018%)
% positive (>= cut-off at 0.005%)	/	/	/	66.7% *P*>0.9999	66.7%
GMR (95% CI)	/	/	/	1.09 (0.64-1.85) Non-inferior *P*= 0.76	/
GM % IFN-γ$^+$CD8$^+$ T cells (95% CI)	/	/	/	0.008% (0.005-0.012%)	0.006% (0.003-0.010%)
% positive (>= cut-off at 0.005%)	/	/	/	31.7% *P*= 0.64	25.0%
GMR (95% CI)	/	/	/	1.33 (0.65-2.70) Non-inferior *P*= 0.43	/
GM % IL-2$^+$CD8$^+$ T cells (95% CI)	/	/	/	0.004% (0.003-0.005%)	0.004% (0.003-0.006%)
% positive (>= cut-off at 0.005%)	/	/	/	28.3% *P*= 0.81	25.0%
GMR (95% CI)	/	/	/	1.02 (0.69-1.50) Non-inferior *P*= 0.92	/
M-specific T cell responses on flow cytometry					
N	/	/	/	60	36
GM % IFN-γ$^+$CD4$^+$ T cells (95% CI)	/	/	/	0.007% (0.005-0.010%)	0.009% (0.005-0.016%)
% positive (>= cut-off at 0.005%)	/	/	/	36.7% *P*= 0.67	41.7%
GMR (95% CI)	/	/	/	0.79 (0.41-1.52) Inconclusive *P*= 0.48	/
GM % IL-2$^+$CD4$^+$ T cells (95% CI)	/	/	/	0.006% (0.004-0.007%)	0.006% (0.004-0.009%)
% positive (>= cut-off at 0.005%)	/	/	/	46.7% *P*>0.9999	47.2%
GMR (95% CI)	/	/	/	0.90 (0.59-1.38) Inconclusive *P*= 0.63	/
GM % IFN-γ$^+$CD8$^+$ T cells (95% CI)	/	/	/	0.006% (0.004-0.009%)	0.005% (0.003-0.008%)
% positive (>= cut-off at 0.005%)	/	/	/	25.0% *P*= 0.62	19.4%
GMR (95% CI)	/	/	/	1.25 (0.66-2.35) Non-inferior *P*= 0.49	/
GM % IL-2$^+$CD8$^+$ T cells (95% CI)	/	/	/	0.004% (0.003-0.005%)	0.004% (0.003-0.006%)
% positive (>= cut-off at 0.005%)	/	/	/	23.3% *P*>0.9999	25.0%
GMR (95% CI)	/	/	/	0.95 (0.66-1.37) Non-inferior *P*= 0.79	/
IFN-γ, interferon-gamma; IL-2, interleukin-2; CI, confidence interval; GMR, geometric mean ratio; S, spike protein; N, nucleocapsid protein; M, membrane protein.					

Extended Table 4. Unsolicited adverse events within 28 days of vaccination in healthy adolescent safety population.			
	BNT162b2 (N = 116)	**CoronaVac (N = 123)**	**Overall (N = 239)**
Summary of adverse events and severe adverse events			
Any adverse event	22 (0.190)	8 (0.065)	30 (0.126)
Grade 1	18 (0.155)	8 (0.065)	26 (0.109)
Grade 2	4 (0.034)	0 (0.000)	4 (0.017)
Grade 3	0 (0.000)	0 (0.000)	0 (0.000)
Severe	0 (0.000)	0 (0.000)	0 (0.000)
Specific adverse events			
Chest pain	4 (0.034)	0 (0.000)	4 (0.017)
N, total number of participants in adolescent healthy safety population. Data are number of events (events per participant).			

Extended Table 5. Multiple regression analysis of baseline variables and sVNT percent inhibition.

	Adolescent B sVNT percent inhibition			Adolescent C sVNT percent inhibition		
Variable	**Estimate**	**95% CI (asymptotic)**	***P*-value**	**Estimate**	**95% CI (asymptotic)**	***P*-value**
Age	0.5	-1.5, 2.5	0.62	-1.5	-3.7, 0.8	0.20
Male sex	1.1	-3.6, 5.9	0.64	-2.8	-11.4, 5.9	0.53
Han Chinese	-3.7	-9.4, 1.9	0.20	/	/	/
WBC	0.5	-0.9, 2.0	0.47	0.5	-3.0, 4.0	0.78
ALC	3.4	-1.2, 7.9	0.14	-2.2	-10.4, 6.0	0.60
Hemoglobin	-0.2	-2.5, 2.1	0.88	2.6	-0.6, 5.7	0.11
Height	-13.7	-53.0, 25.5	0.49	-24.1	-79.4, 31.2	0.39
Weight	0.01	-0.2, 0.2	0.91	0.2	-0.2, 0.5	0.43

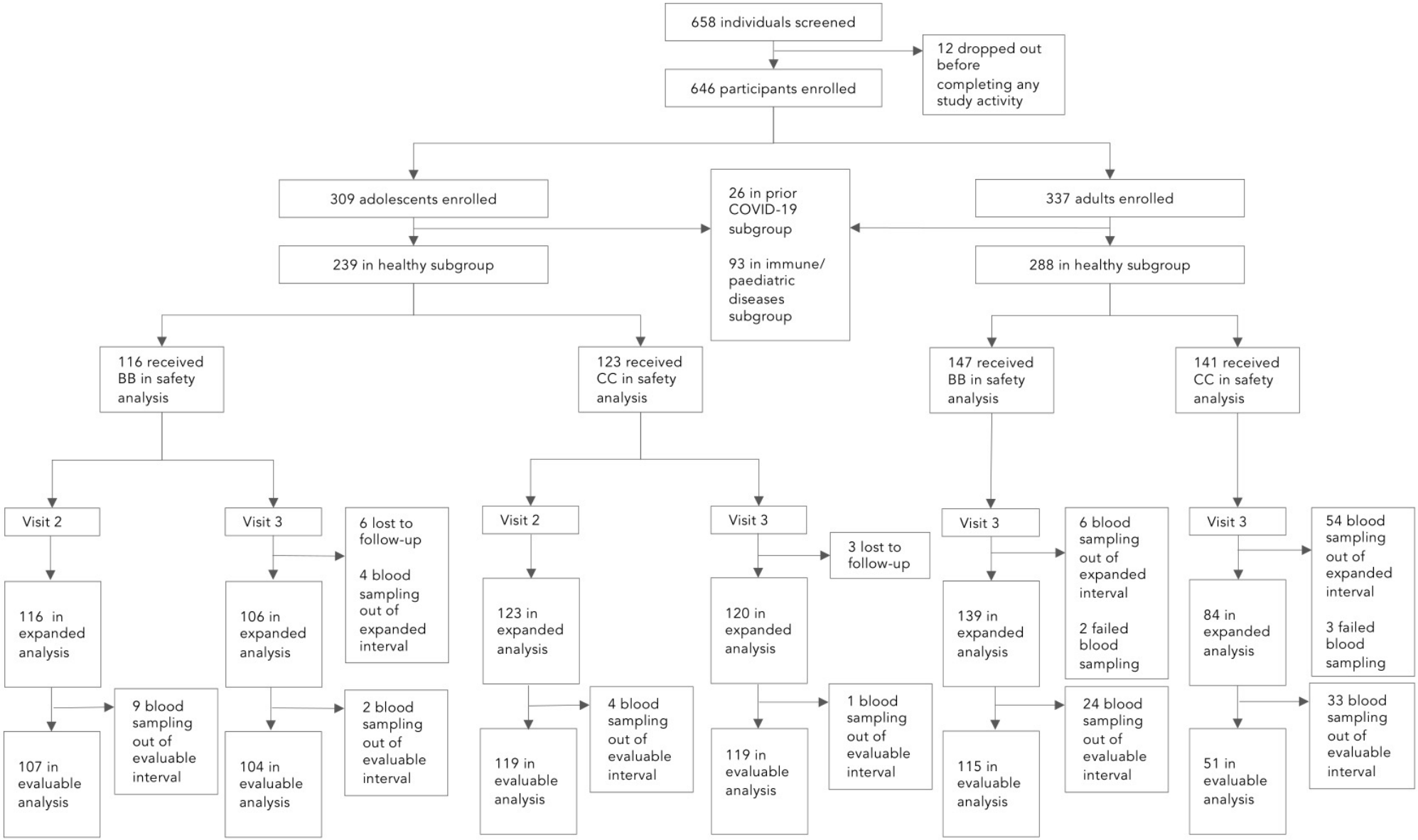
B, BNT162b2 1 dose; C, CoronaVac 1 dose; WBC, white blood cell count; ALC, absolute lymphocyte count.

Extended Table 6. Differences in baseline variables including anthropometric and haematological parameters for adolescents by vaccine regimen.

Variable	Difference between means (+/- SEM)	*P*-value
White cell count	-0.34 (+/- 0.19)	0.07
Absolute lymphocyte count	-0.15 (+/- 0.07)	0.04
Hemoglobin	-0.06 (+/- 0.15)	0.70
Height	0.003 (+/- 0.01)	0.79
Weight	0.99 (+/- 1.73)	0.57

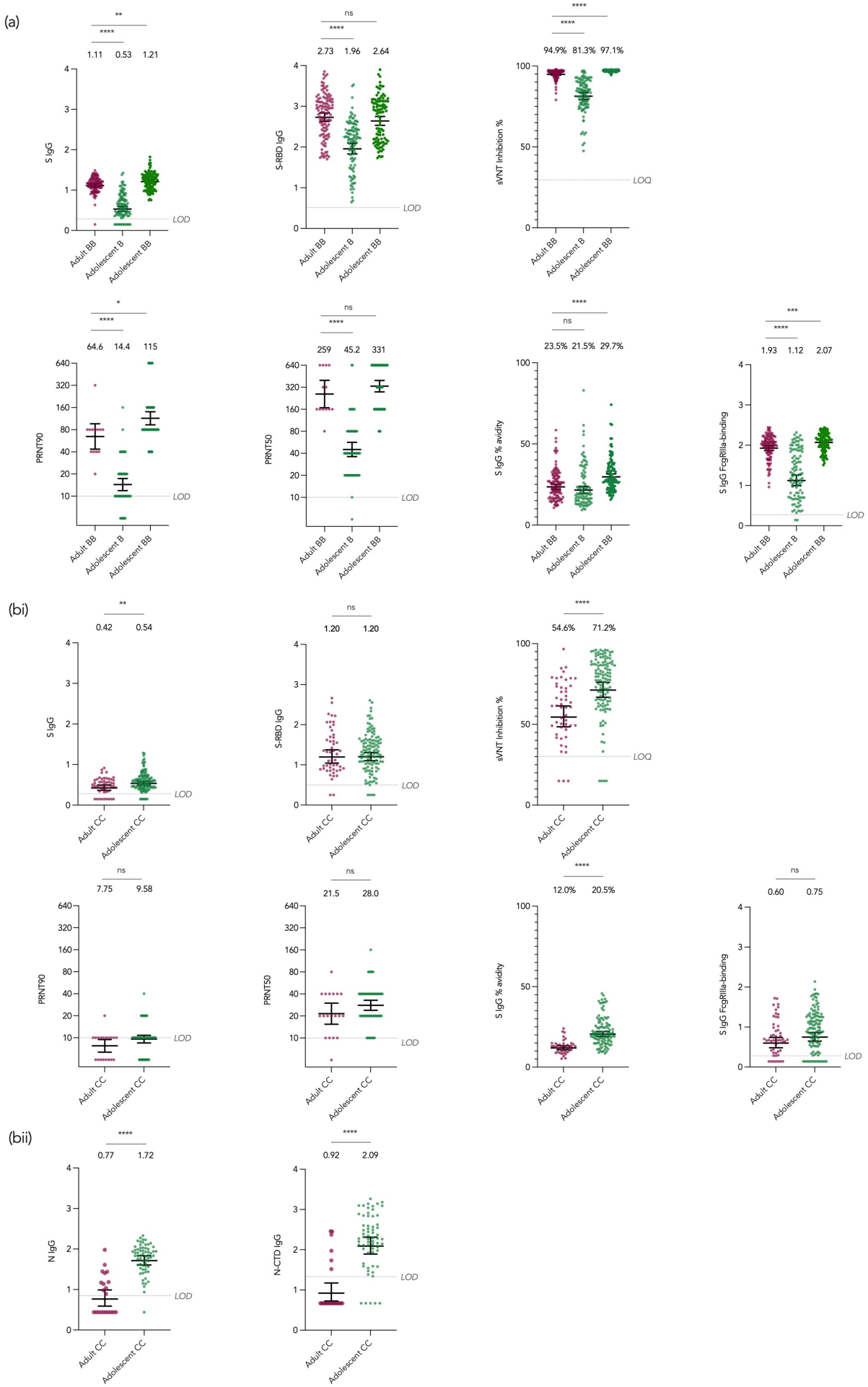
WBC, white blood cell count; ALC, absolute lymphocyte count.
P-values derived from unpaired *t* test. $P<0.01$ regarded as significant.

Extended Data Fig. 1



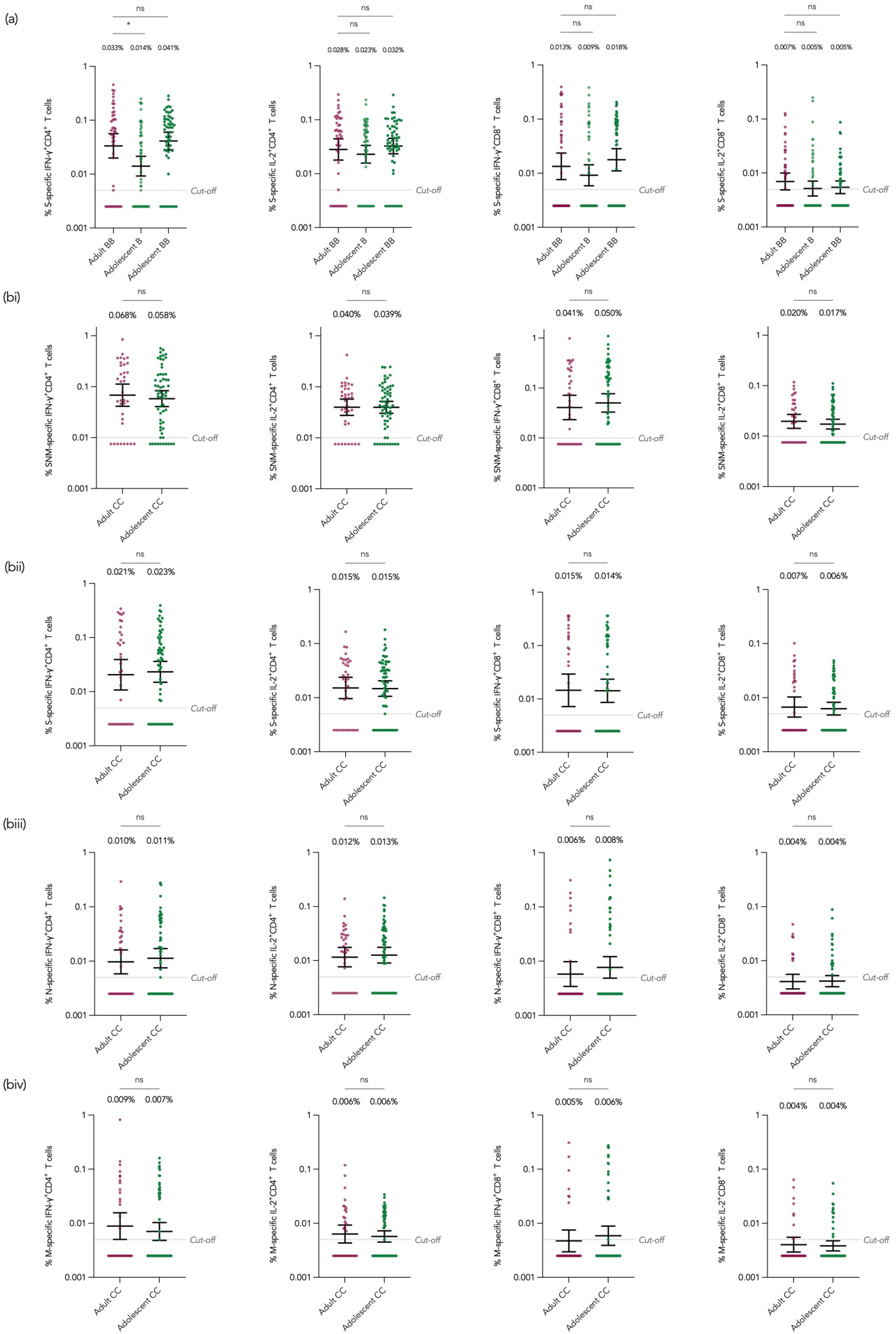
Extended Data Fig. 1 | Flow diagram of study participants. There were 658 volunteers who were screened, with a total of 646 participants consisting of 309 and 337 adolescents aged 11-17 years and adults aged ≥18 years at the time of dose 1, respectively, who consented and were enrolled. This present interim analysis focuses on healthy participants. Therefore, 26 were enrolled into another prior infection and 93 in severe paediatric illness sub-studies after review of clinical history and laboratory screening results. There were 239 adolescent and 288 adult participants (*N*=527) in this interim analysis and the reactogenicity/safety analyses. The evaluable analysis population included uninfected participants who had no major protocol deviations and a valid result. The evaluable analysis set included 223 adolescents and 166 adults included in for the primary immunogenicity outcomes after 2 doses. For the corresponding modified intention-to-treat analysis, there were 226 adolescents and 223 adults in the expanded analysis population. B, 1 dose of BNT162b2; BB, 2 doses of BNT162b2; C, 1 dose of CoronaVac; CC, 2 doses of CoronaVac; visit 2, blood sampling after B or C and immediately before BB or CC; visit 3, after BB or CC.

Extended Data Fig. 2



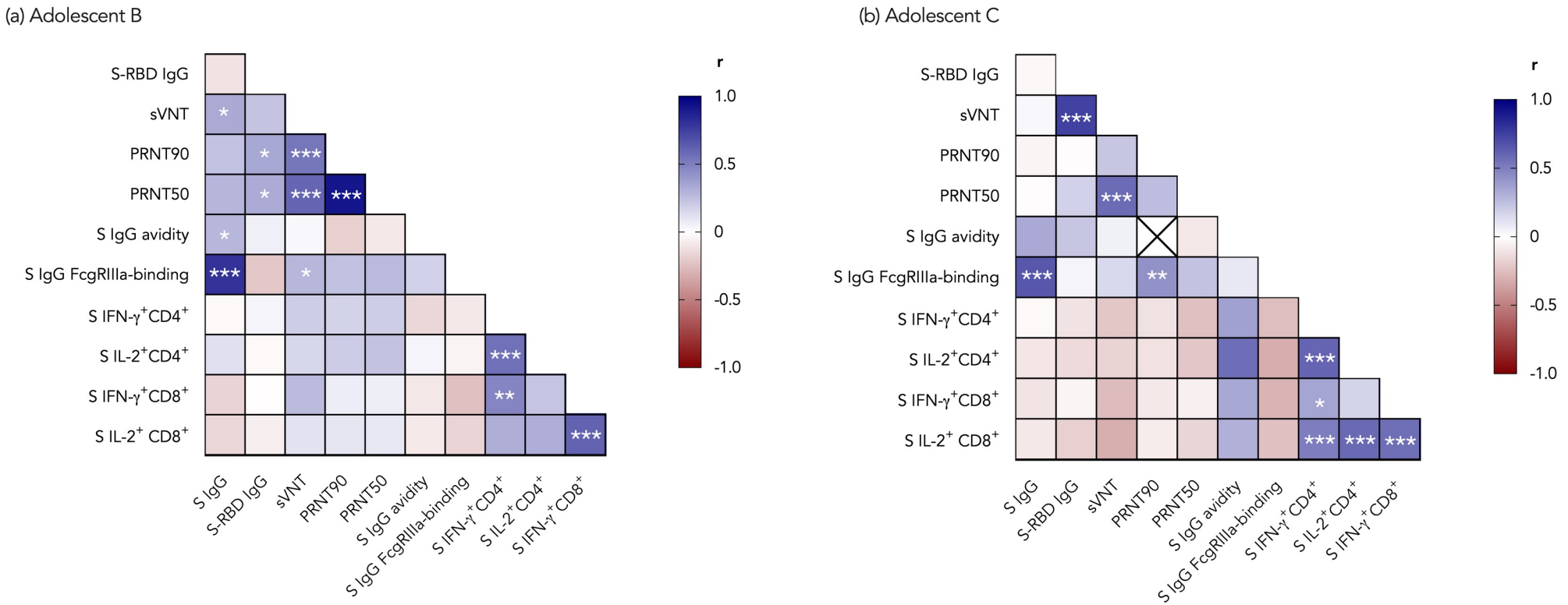
Extended Data Fig. 2 | Humoral immunogenicity after (a) BNT162b2 and (b) CoronaVac in adolescents versus adults. **a**, S IgG, S-RBD IgG, sVNT, PRNT90, PRNT50 and S IgG FcγRIIIa-binding but not S IgG avidity were all lower in adolescent B than adult BB (all $P<0.0001$). S IgG ($P=0.0036$), sVNT ($P<0.0001$), PRNT90 ($P=0.018$), S IgG avidity ($P<0.0001$) and S IgG FcγRIIIa-binding ($P=0.0005$) were higher in adolescent BB than adult BB. **bi**, S IgG ($P=0.0049$), sVNT ($P<0.0001$) and S IgG avidity ($P<0.0001$) were higher in adolescent CC than adult CC. **bii**, N and particularly N-CTD IgG levels were markedly higher in adolescent CC compared to adult CC, both $P<0.0001$. Data labels and centre lines show GM estimates, and error bars show 95% CI. GM, geometric mean; GMR, geometric mean ratio; CI, confidence interval; B, 1 dose of BNT162b2; BB, 2 doses of BNT162b2; CC, 2 doses of CoronaVac; S, spike protein; RBD, receptor-binding domain; sVNT, surrogate virus neutralization test; PRNT, plaque reduction neutralization test; FcγRIIIa, Fcγ receptor IIIa; N, nucleocapsid protein; CTD, C-terminal domain; *, $P<0.05$; ***, $P<0.001$; ****, $P<0.0001$.

Extended Data Fig. 3



Extended Data Fig. 3 | Cellular immunogenicity after (a) BNT162b2 and (b) CoronaVac in adolescents versus adults. **a**, Except for S-specific IFN-γ^+CD4$^+$ T cell response, which was lower in adolescent B than adult BB (*P*=0.01), there were no other differences in the other SNM-specific or S-, N-, M-specific T cell parameters between **a-biv**, adolescent B vs BB vs adult BB and adolescent CC vs adult CC. Data labels and centre lines show GM estimates, and error bars show 95% CI. GM, geometric mean; GMR, geometric mean ratio; CI, confidence interval; B, 1 dose of BNT162b2; BB, 2 doses of BNT162b2; CC, 2 doses of CoronaVac; S, spike protein; N, nucleocapsid protein; M, membrane protein; IFN-γ, interferon-γ; IL-2, interleukin-2. *, *P*<0.05.

Extended Data Fig. 4



Extended Data Fig. 4 | Correlation matrix of spike-specific immunogenicity outcomes by vaccine type. There was strong correlation within humoral (S IgG with FcγRIIIa-binding, sVNT with PRNT50) and within cellular immunogenicity outcomes (S-specific IFN-γ^+CD4$^+$ with IL-2$^+$CD4$^+$ and IFN-γ^+CD8$^+$; IL-2$^+$CD8$^+$ with IFN-γ^+CD8$^+$) for both vaccines (**a**, BNT162b2; **b**, CoronaVac). S, spike protein; RBD, receptor-binding domain; sVNT, surrogate virus neutralization test; PRNT, plaque reduction neutralization test; FcγRIIIa, Fcγ receptor IIIa; IFN-γ, interferon-γ; IL-2, interleukin-2. Blue, strong positive correlation (r=1); red, strong negative correlation (r=-1); white, no correlation (r=0); *, P<0.01; **, P<0.001; ***, P<0.0001.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- COVAC01StatisticalAnalysisPlanV1.1.pdf
- COVAC01ProtocolV6.1.pdf