Immunogenicity, efficacy, and safety of SARS-CoV-2 vaccine dose fractionation: a systematic review and meta-analysis

Bingyi Yang (yangby@hku.hk)
The University of Hong Kong https://orcid.org/0000-0002-0811-8332
Xiaotong Huang
The University of Hong Kong
Huizhi Gao
The University of Hong Kong
Nancy Leung
HKU
Tim Tsang
The University of Hong Kong https://orcid.org/0000-0001-5037-6776
Benjamin Cowling
University of Hong Kong https://orcid.org/0000-0002-6297-7154

Article

Keywords: SARS-CoV-2, vaccine, fractional dose

Posted Date: June 2nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1571821/v2

Immunogenicity, efficacy, and safety of SARS-CoV-2 vaccine dose fractionation: a systematic review and meta-analysis

Bingyi Yang[1], Xiaotong Huang[1], Huizhi Gao[1], Nancy H. Leung[1], Tim K. Tsang[1,2], Benjamin J. Cowling[1,2]

Affiliations:

1. WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China
2. Laboratory of Data Discovery for Health Limited, Hong Kong Science and Technology Park, New Territories, Hong Kong, China

Corresponding author:

Benjamin J. Cowling, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 7 Sassoon Road, Pokfulam, Hong Kong

Tel: +852 3917 6711; Email: bcowling@hku.hk

or

Bingyi Yang, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 7 Sassoon Road, Pokfulam, Hong Kong

Tel: +852 3917 6911; Email: yangby@hku.hk

Word count: (Abstract: 155)

(Main text: 2, 933)

Abstract

Background: Dose fractionation of Coronavirus Disease 2019 (COVID-19) vaccine could effectively accelerate global vaccine coverage, while supporting evidence of efficacy, immunogenicity, and safety are unavailable, especially with emerging variants.

Methods: We systematically reviewed clinical trials reported dose-finding results and estimated the dose-response relationship of neutralizing antibodies (nAbs) of COVID-19 vaccines using generalized additive model. We predicted the vaccine efficacy against both ancestral and variants, using previously reported correlates of protection and cross-reactivity. We also reviewed and compared seroconversion to nAbs, T-cell responses and safety profiles between fractional and standard dose groups.

Results: We found that dose fractionation of mRNA and protein subunit vaccines could induce SARS-CoV-2 specific nAbs and T-cells that confer a reasonable level of protection (i.e., vaccine efficacy > 50%) against ancestral strains and variants up to Omicron. Safety profiles of fractional doses were non-inferior to the standard dose.

Conclusion: Dose fractionation of mRNA and protein subunit vaccines may be safe and effective.

Introduction

Three years into the pandemic, COVID-19 continues to threaten global health with emerging variants. While vaccinations are effective in preventing hospitalizations and deaths [1,2], there has been unequal distribution of vaccinations across the globe. Despite that the current vaccine supply would cover most of the global population, a portion of the supply were prioritized for the fourth or fifth dose in high income countries, while only 15.7% of people in lower income countries had received at least one vaccine dose as of 16 May 2022 [3]. Dose fractionation of vaccines has been previously recommended to ease global supply shortage and accelerate vaccine coverage in low-income countries, where a larger proportion of the population could have access to vaccination while each individual would receive a lower vaccine dose [4,5]. However, uncertainties and concerns about the vaccine efficacy using fractional doses against SARS-CoV-2 ancestral strains and emerging variants of concern (VoCs) [6-8], and the potential differences between vaccine platforms, hindered the endorsement for dose fractionation of COVID-19 vaccines [9,10]. Nevertheless, a half-dose of the original Moderna vaccine has been recommended for the booster dose for adults who are not moderately and severely immunocompromised [11].

Here, we conducted a systematic review and meta-analysis of phase I/II trials that reported dose-finding results of immunogenicity and safety profiles for COVID-19 vaccines (detailed search terms in Table S1). We estimated the pooled dose-response relationship of neutralizing antibodies (nAbs) against the ancestral strain, which were then used to predict the potential VE of fractional doses against infections of the ancestral strain and VoCs using a hypothesized relation between nAbs and protection [12,13] . We also reviewed the differences in seroconversion of nAbs, T-cell mediated immune responses and safety profile

between fractional and standard dose (i.e., doses used for final products or phase III trials) groups, to further assess the differences in immunogenicity and safety after receiving fractional and standard doses.

Methods

Search strategy and study selection

We searched peer-reviewed publications on clinical trials of SARS-CoV-2 vaccines in PubMed on 9 December 2021. We searched with the following terms: (SARS-CoV-2 OR COVID-19) AND (vaccine AND dose) AND (antibod* OR immun*) (Table S1). We included dose-escalation studies that reported safety, neutralizing antibodies (nAbs, which were measured by $PRNT_{50}$ and/or sVNT), and/or T-cell mediated immunity among healthy individuals received SRAS-CoV-2 vaccines (Tables S2-4). We excluded 1) studies did not report immunological response or only reported binding antibody; 2) studies without dose-escalation; 3) studies on non-human hosts; 4) studies on participants with specific health conditions (e.g., cancer, organ transplantation) or pregnancy; 5) studies specifically designed for hybrid immunity (i.e., natural infection or heterogenous vaccinations); and 6) reviews or commentaries (Figure S1). We assessed the quality of included studies using the Cochrane Risk of Bias tool 2.0 for randomized trials [14] (Figure S2).

Data extraction and processing

Two reviewers (BY and XH) independently screened the titles and full texts of articles according to the inclusion and exclusion criteria. For each included study, we extracted relevant information of the vaccines and participants onto a standardized form, which

includes vaccine name, manufacture, platform, dose fraction, vaccination and sampling schedule, age group, and sizes of vaccinated subjects. Dose fraction ($F_{i,j}$) was defined as the ratio of each examined dose group ($d_{i,j}$) and the standard dose ($d_{ref,j}$, defined as the dose selected for the approved vaccine product or phase III trials) for each study (j):

$$F_{i,j} = \frac{d_{i,j}}{d_{ref,j}} \quad (1)$$

Differences in seroconversion of neutralizing antibodies after fractional and standard dose

We compared the seroconversion proportion to nAbs against ancestral strains after receiving fractional doses compared with the standard dose group, where seroconversion was predefined by each study as at least four-fold increase in nAbs and/or changing from negative to positive after vaccinations (details about definitions for positive threshold and seroconversion were shown in Table S3). We chose to estimate the pooled risks ratio of seroconversion over the pooled proportion of seroconversion, to minimize the impacts of measurement variations between laboratories. Sample size and the number of seroconverted participants were extracted for each dose group, which were then used to estimate the pooled log risk ratio of seroconversion between fractional and standard dose group using random effects (RE) model, stratified by vaccine type. We fitted mixed effects meta-regressions to assess the effects of vaccine platform and dose fractions on seroconversion, after accounting for age group and assay methods. We also repeated the above analysis for higher dose group, which results can be found in our data repository.

Dose-response relationship of neutralizing antibodies

For each study j, we extracted the mean ($\mu_{i,j}$) and standard deviations ($\sigma_{i,j}$) of nAbs titers in different dose groups i; if not reported, we estimated $\mu_{i,j}$ and $\sigma_{i,j}$ from 1) individual data points, or 2) median, interquartile (IQR) and sample sizes[15]. We then standardized the vaccine-induced nAbs level ($z_{i,j}$) using the nAbs measured in convalescent sera ($\mu_{c,j}$) for each study:

$$z_{i,j} = \frac{\mu_{i,j}}{\mu_{c,j}} \quad (2)$$

We summarized standardized nAbs among different dose groups (i.e., fractional, standard, and higher dose groups) at different time points (i.e., days after 1 or 2 doses). To quantify the non-linear dose-response relationship of vaccination and the standardized nAbs ($z_{i,j}$), we fitted a generalized additive model (GAM; Table S5) that accounted for the vaccine platform (V), vaccine schedule (i.e., total dosages D and days after full vaccination $T_{i,j}$), age group (A = children, adult, or elderly) and antigen used for neutralizing assay (M = live or pseudo virus):

$$\log_2 z_{i,j} = \beta_0 + \beta_T s(T_{i,j}) + \beta_F s(\log_2 F_{i,j}) + \beta_V V_j + \beta_D D_{i,j} + \beta_A A_{i,j} + \beta_M M_{i,j} \quad (3)$$

With estimates from equation 3, we predicted the standardized nAbs (assuming measured by live virus and in adults; same for the following) against SARS-CoV-2 ancestral strain 14 days after fully vaccinated (i.e., 1 dose for vector and 2 for the rest) with fractional doses ($F_{i,j}$) for different vaccine platforms. We validated our model predictions and raw data and performed ten-fold cross-validation (Figure S3 and Table S6).

Vaccine efficacy predicted from neutralizing antibodies

We applied the established CoP protection of standardized nAbs [12,13] to predict the dose-fractioning vaccine efficacy (Φ_i) against symptomatic infections of SARS-CoV-2 ancestral strain for different vaccine platform (V):

$$\Phi_{i,V,E} = \frac{1}{1 + e^{-k_E \log_{10} \frac{z_{i,V}}{z_{50,E}}}} \quad (4)$$

We obtained the log-transformed 50% protective efficacy ($\log_{10} z_{50,E}$) and steepness parameter k_E for both symptomatic and severe infection from the previous study [12]. $z_{i,V}$ is the standardized nAbs at 14 days after fully vaccinated of fractional doses ($F_{i,j}$) for each vaccine platform (V), which was estimated from equation 3 with coefficients shown in Table S5.

We used previously reported [6,13] fold of reduction (δ_S; Table S7) in nAbs to estimate the level of standardized nAbs ($\delta_S z_{i,V}$) against the variant S, which was then applied to equation 4 to predict the vaccine efficacy of dose fractioning against infections of SARS-CoV-2 variant of concerns (VoCs). To validate our predicted vaccine efficacy against VoCs (Supplementary Figure 9), we compared the predicted vaccine efficacy against symptomatic infections after standard dose and observations (Table S8) reported previously by Pearson correlation. Standard doses were used for comparison since there were no empirical data regarding half-dose.

T-cell responses

Since assays and measurements used for T-cell mediated responses vary across studies, we reviewed if T-cell responses elicited by dose-fractioning vaccines 1) would be higher than

that at pre-vaccination level and 2) would be lower than that elicited by the standard dose vaccine within the same study. Briefly, we extracted mean ($\bar{x}_{i,j,k}$; log-transformed if originally measured in log-scale; same for SE), standard error (SE, $\hat{\sigma}_{\bar{x}_{i,j,k}}$) and sample size ($n_i$) of specific measurement k for T-cell responses for each dose group or reference group (i.e., pre-vaccination or post standard dose vaccination) i in study j. Specific measurement (k) includes T-cell types (i.e., CD4+ or CD8+) and/or cytokines for T helper type 1 (Th1, including interferon-γ (IFN- γ), tumor necrosis factor (TNF- α) and Interleukin-2 (IL-2)) and T helper type 2 (Th2, including IL-4, IL-5, IL-13). If mean and SE were not reported, we estimated these metrics from individual original data points or median, IQR and sample sizes [15]. We determined the statistical significance of difference in (log-)means ($\Delta_{i,j,k}$) assuming it follows a normal distribution.

$$\overline{\Delta}_{i,j,k} = \bar{x}_{i,j,k} - \bar{x}_{ref,j,k} \quad (5)$$

$$\hat{\sigma}_{\overline{\Delta}_{i,j,k}} = \sqrt{\frac{\hat{\sigma}_{\bar{x}_{i,j,k}}^{2}}{n_i} + \frac{\hat{\sigma}_{\bar{x}_{ref,j,k}}^{2}}{n_{ref}}} \quad (6)$$

Safety

We compared the safety profiles after receiving fractional dose compared with the standard dose group. We extracted the sample size and the number of adverse events (AEs, i.e., solicited local and/or systemic events, unsolicited events, and any AEs) for each dose group. Individual manifestations within each AE category were extracted and assessed. We estimated the pooled log risk ratio of experiencing AEs between fractional and standard dose group using RE model and stratifying by specific AE and vaccine platform. We calculated the I^2 to measure the heterogeneity of the included estimates. We also repeated the above analysis for higher dose group, which results can be found in our data repository.

Results

In total 1,733 records were returned from PubMed search with 44 duplicates. After titer and abstract screening, 136 records were eligible for full-text screen (Figure S1). Thirty-eight studies were included in the analyses [16-53], among which inactivated vaccines (29%, n = 11) were studied the most, followed by protein subunit ("subunit" hereafter; 26%, n = 10), mRNA (24%, n = 9), non-replicating viral vector ("vector" hereafter; 13%, n = 5) and others (Figure S1 and Table S2). We found overall low risks of bias of the included studies, expect that seven adopted the non-randomized, and non-double-blinded design (Figure S2) [16,26,27,32,37,39,53].

Seroconversion of neutralizing antibodies after fractional doses

We estimated the pooled risk ratio (RR) of the seroconversion against ancestral strains among individuals who completed fractional and standard dose from 14 studies of 9 vaccines (Figure 1). The probability of seroconversion to ancestral strains was 2.1% (95% confidence interval (CI) 0.4% to 3.6%; I^2= 52.0%, P-value < 0.01) lower among individuals with fractional doses compared to standard doses within the same trial. However, we found no association between dose fractionation (1.4%, 95% CI, -20.4% to 29.3% per fold increase in dose) and seroconversion proportions between lower and standard dose groups after accounting for vaccine platform, age group and assay methods (i.e., live or pseudo virus) (Table S9).

Dose-relationship of neutralizing antibodies and predicted vaccine efficacy

Twenty-four studies reported nAbs against live (n = 20) and/or pseudo (n = 7) ancestral viruses from both post-vaccination and convalescent sera (Figures S4-6 and Table S3). We estimated that prime with one half-dose would elicit less than 10% of nAbs in convalescent sera, while prime-boost with two half-doses elicited higher nAbs than a single standard dose across all platforms (Figure 2A and Figures S3-7).

We estimated that two half-dose mRNA vaccines would elicit 2.6 (95% CI, 2.1 to 3.3, measured on day 14) fold of the nAbs against the ancestral strain in convalescent sera (Figure 2A), which is expected to prevent 97% (95% CI, 95% to 97%) of symptomatic infections of the ancestral strains, respectively (Figure 2B). Whereas two half-dose inactivated vaccines would elicit 0.28 (95% IC 0.20 to 0.37) -fold of nAbs against the ancestral strains in convalescent sera, corresponding to 61% (95% CI, 51% to 70%) and 95% (95% CI, 92% to 96%) efficacy against symptomatic and severe infections of the ancestral strains, respectively. Overall, our predictions suggested that the reduction in vaccine efficacy was smaller than dose fractionation across all vaccine platforms (Figure 2C); half-doses may provide more than half of protection efficacy of standard doses.

Further incorporating the reported fold reduction in of vaccine-induced nAbs against VoCs (Table S7)[6,13], we projected that two half-dose mRNA vaccines would confer the highest efficacy against symptomatic infections of VoCs (94%, 95% CI, 92% to 95% against Alpha, 63%, 54% to 70% against Beta, 85%, 79% to 89% against Gamma, 83%, 78% to 87% against Delta and 32%, 26% to 40% against Omicron), followed by subunit, vector and inactivated vaccines (Figure 3 and Figure S8). Our predicted efficacy against symptomatic infections of

VoCs for standard dose highly correlated (Pearson correlation 0.705, p-value < 0.01; Figure S9) with empirical data [54-64], while we were not able to validate predictions for fractional doses due to lack of data. Results from ten-fold validations further supported our model fitting (Table S6).

T-cell responses after fractional doses

We first reviewed whether T-cell mediated immune responses elicited by dose fractioning vaccines would be higher than pre-vaccination level. All 7 studies of 5 vaccines reported significant increase in SARS-CoV-2 specific CD4+/CD8+ or CD4+ T helper type 1 (Th1) responses after vaccinated with fractional doses compared to pre-vaccination (Figure 4A), which were all biased to Th1 cells.

We then reviewed whether T-cell responses would be lower than that elicited by the standard dose vaccine. Three vaccines (BNT162b1[30,37], MVC-COV1901[26] and Sf9 cells[31]) reported that dose fractionation elicited similar level of CD4+ and/or CD8+ T-cells compared to standard dose (Figure 4B). Quarter-dose of mRNA-1273 [16,27] was reported to induce significantly lower CD4+ Th1 cells compared to standard dose, while half-dose of BBV152 were reported to induce significantly higher Th1 cytokines in one of two trials. We also compared the cellular responses between standard and higher dose groups and found no evidence for dose-dependent relationship for 7 out of 9 vaccines (Figure S10).

Safety profiles after fractional doses

We reviewed the safety profile for 34 studies and found that, compared to standard dose group, people in the fractional dose groups tended to experience adverse events at similar or lower frequency (Figures 11-16). Particularly, the risk of experiencing solicited, and unsolicited adverse events were 9.5% (95% CI, 3.9% to 14.8 %) and 24.4% (3.9% to 41.1%) lower in individuals who received factional dose of mRNA vaccines compared to standard doses (Figures 14-15). One inactivated (BBIBP-CorV in children [46]) and two subunit (NVX-CoV2373 and Livzon in adults [22,38]) vaccines reported higher risk of solicited systemic reactions in groups that received lower dose than the standard dose.

Discussion

Our findings suggested that vaccine-induced nAbs varied substantially across dose fractions, number of dosages, and vaccine platforms. For vaccine platforms (e.g., mRNA and subunit) which standard doses could elicit higher nAbs levels than convalescent sera, fractionation of prime-boost doses could induce robust nAbs against the ancestral strains and similar seroconversion proportion with standard doses. nAbs induced by fractional vaccines of mRNA and subunit were predicted to confer $\geq$ 65% efficacy against symptomatic infections of SARS-CoV-2 variants, except for Beta and Omicron. Fractionation of vaccine doses seemed to be safe and induce robust Th1 biased T-cell responses that were similar to standard doses except for mRNA-1273.

We found that dose fractionation of COVID-19 vaccines would induce, though lower than standard doses, detective nAbs against ancestral strains. Based on previously established CoP [12,13,65], these nAbs may confer reasonable protection (i.e., > 50%) against symptomatic

infections of ancestral strains, but not the subsequent VoCs, especially Omicron. Previous modelling study suggested that dose fractionation could be a cost-effective strategy in low-income countries, if vaccination could confer at least 50% of protection against symptomatic infections of variants with low or moderate transmissibility (i.e., basic reproduction number R_0 < 5) [66]. Given these findings, our results of nAbs and vaccine efficacy predictions suggested that dose fractionation could have been cost-effective strategy to control the emergence of some early VoCs (e.g., Alpha and Delta), but not for the currently circulating Omicron given the significant immunity breakthrough [6,7] and higher transmissibility [67].

While there is no established correlate of protection against severe COVID, we found that fractional doses of most studied vaccines could induce detective and likely robust T-cell responses, which may contribute to protection against severe outcomes given that SARS-CoV-2 specific T-cells could broadly cross-react to a range of VoCs (including Omicron) and were associated with better outcomes [68,69]. Therefore, dose fractionation of COVID-19 vaccines might still be able to avert a considerable number of hospitalizations and deaths, even with the emergence of new variants with higher rates of breakthrough infections.

We were not able to assess the durability of the immune responses elicited by fractional doses of COVID-19 vaccines, as most trials reported limited follow up that was typically just one month after vaccination. Therefore, our efficacy estimates may only be indicative for short-term protection. Waning SARS-CoV-2 specific aAbs, T-cells and vaccine efficacy (against both ancestral and VoCs) may be expected, as suggested by evidence from individuals receiving standard doses after 6 months [7,70-72]. For standard doses, both

281 homogeneous and heterogenous boosters could substantially increase nAbs and vaccine
282 efficacy against VoCs [8], while such data were lacking for fractional doses.
283
284 To minimize the impacts of measurement variations between laboratories, we compared
285 the differences in seroconversion of nAbs and T-cell responses within each trial and
286 quantified the dose-relationship using nAbs that were standardized to convalescent sera.
287 Calibration to recommended international standard may further reduce the between
288 laboratory variations, which was, however, not reported by the included trials.
289
290 We did not look at the nAbs induced by individual vaccine manufacturers due to limited
291 data, while we found consistent seroconversion proportion and dose-relationship within
292 platform (Figures 3-7). Nevertheless, disparities in nAbs levels and durability were reported
293 for individual vaccines from the same platform (e.g., mRNA-1273 vs. BNT162b1 vaccines [9]).
294
295 Our study only focused on the immunogenicity and safety and the projected efficacy of dose
296 fractionation of COVID-19 vaccines, and therefore findings should be interpreted within this
297 scope. Endorsement of dose fractionation of vaccines by regulatory agencies would likely
298 need stronger efficacy data, and other considerations would include the evolving supply
299 situation, logistics restrictions, and vaccine communications.
300
301 To summarise, fractionation of vaccine doses, especially mRNA and protein subunit
302 vaccines, are safe and would induce antibody and T-cell responses that likely confer a
303 reasonable level of protection against severe infections of SARS-CoV-2 ancestral and VoCs
304 up to Omicron. The use of vaccines with lower antigen content earlier in the pandemic

might have been an efficient approach to save even more lives, while further clinical investigation of fractional booster doses would certainly be worthwhile.

Data availability

All data were collected from publicly available literatures, with detailed description in the Methods and Supplementary Tables. Data used for the analysis can be assessed at: https://github.com/byyangyby/fractional_dose_review.

Code availability

The authors declare that all codes for analyzing the data are made available at https://github.com/byyangyby/fractional_dose_review.

Acknowledgements

This project was supported by the Theme-based Research Scheme (Project No. T11-712/19-N) of the Research Grants Council of the Hong Kong SAR Government. BJC also acknowledges the support AIR@InnoHK administered by Innovation and Technology Commission of the Government of the Hong Kong Special Administrative Region.

Author contributions

All authors meet the ICMJE criteria for authorship. BY and BJC conceived the study. BY and XH performed the literature review and screening. BY, XH and HG extracted data. BY analyzed the data and wrote the first draft of the manuscript. All authors provided critical review and revision of the text and approved the final version.

329

330 **Completing interest statement**

331 B.J.C. consults for AstraZeneca, GSK, Moderna, Roche, Sanofi Pasteur, and Pfizer. The

332 remaining authors declare no competing interests.

References

1. Haas EJ, McLaughlin JM, Khan F, et al. Infections, hospitalisations, and deaths averted via a nationwide vaccination campaign using the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine in Israel: a retrospective surveillance study. *Lancet Infect Dis* 2022; **22**(3): 357-66.
2. Mesle MM, Brown J, Mook P, et al. Estimated number of deaths directly averted in people 60 years and older as a result of COVID-19 vaccination in the WHO European Region, December 2020 to November 2021. *Euro Surveill* 2021; **26**(47).
3. Mathieu E, Ritchie H, Ortiz-Ospina E, et al. A global database of COVID-19 vaccinations. *Nat Hum Behav* 2021; **5**(7): 947-53.
4. Cowling BJ, Lim WW, Cobey S. Fractionation of COVID-19 vaccine doses could extend limited supplies and reduce mortality. *Nat Med* 2021; **27**(8): 1321-3.
5. World Health Organization. Fractional dose yellow fever vaccine as a dose-sparing option for outbreak response. 2016.
6. Carreno JM, Alshammary H, Tcheou J, et al. Activity of convalescent and vaccine serum against SARS-CoV-2 Omicron. *Nature* 2021.
7. Andrews N, Stowe J, Kirsebom F, et al. Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. *New England Journal of Medicine* 2022.
8. Cheng SMS, Mok CKP, Leung YWY, et al. Neutralizing antibodies against the SARS-CoV-2 Omicron variant BA.1 following homologous and heterologous CoronaVac or BNT162b2 vaccination. *Nat Med* 2022.
9. Wilder-Smith A, Desai S, Cravioto A, Nohynek H, Hombach J. Caution before fractionating COVID-19 vaccines. *Nature Medicine* 2021; **27**(11): 1856-7.
10. World Health Organization. Interim statement on dose-sparing strategies for COVID-19 vaccines (fractionated vaccine doses). 2021. https://www.who.int/news/item/10-08-2021-interim-statement-on-dose-sparing-strategies-for-covid-19-vaccines-(fractionated-vaccine-doses) (accessed 6 March 2022).
11. Centers for Diseases Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines | CDC. May 23, 2022. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#considerations-covid19-vax-booster (accessed June 1 2022).
12. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021; **27**(7): 1205-11.
13. Cromer D, Steain M, Reynaldi A, et al. Neutralising antibody titres as predictors of protection against SARS-CoV-2 variants and the impact of boosting: a meta-analysis. *Lancet Microbe* 2022; **3**(1): e52-e61.
14. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898.
15. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; **14**: 135.
16. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. *N Engl J Med* 2020; **383**(25): 2427-38.

17. Chappell KJ, Mordant FL, Li Z, et al. Safety and immunogenicity of an MF59-adjuvanted spike glycoprotein-clamp vaccine for SARS-CoV-2: a randomised, double-blind, placebo-controlled, phase 1 trial. *Lancet Infect Dis* 2021.
18. Che Y, Liu X, Pu Y, et al. Randomized, double-blinded and placebo-controlled phase II trial of an inactivated SARS-CoV-2 vaccine in healthy adults. *Clin Infect Dis* 2020.
19. Chu L, McPhee R, Huang W, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. *Vaccine* 2021; **39**(20): 2791-9.
20. Ella R, Reddy S, Jogdand H, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. *Lancet Infect Dis* 2021; **21**(7): 950-61.
21. Ella R, Vadrevu KM, Jogdand H, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. *Lancet Infect Dis* 2021; **21**(5): 637-46.
22. Formica N, Mallory R, Albert G, et al. Different dose regimens of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373) in younger and older adults: A phase 2 randomized placebo-controlled trial. *PLoS Med* 2021; **18**(10): e1003769.
23. Goepfert PA, Fu B, Chabanon AL, et al. Safety and immunogenicity of SARS-CoV-2 recombinant protein vaccine formulations in healthy adults: interim results of a randomised, placebo-controlled, phase 1-2, dose-ranging study. *Lancet Infect Dis* 2021; **21**(9): 1257-70.
24. Guo W, Duan K, Zhang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18 years or older: A randomized, double-blind, placebo-controlled, phase 1/2 trial. *EClinicalMedicine* 2021; **38**: 101010.
25. Han B, Song Y, Li C, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. *Lancet Infect Dis* 2021.
26. Hsieh SM, Liu WD, Huang YS, et al. Safety and immunogenicity of a Recombinant Stabilized Prefusion SARS-CoV-2 Spike Protein Vaccine (MVC-COV1901) Adjuvanted with CpG 1018 and Aluminum Hydroxide in healthy adults: A Phase 1, dose-escalation study. *EClinicalMedicine* 2021; **38**: 100989.
27. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. *N Engl J Med* 2020; **383**(20): 1920-31.
28. Keech C, Albert G, Cho I, et al. Phase 1-2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. *N Engl J Med* 2020; **383**(24): 2320-32.
29. Kremsner PG, Mann P, Kroidl A, et al. Safety and immunogenicity of an mRNA-lipid nanoparticle vaccine candidate against SARS-CoV-2 : A phase 1 randomized clinical trial. *Wien Klin Wochenschr* 2021: 1-11.
30. Li J, Hui A, Zhang X, et al. Safety and immunogenicity of the SARS-CoV-2 BNT162b1 mRNA vaccine in younger and older Chinese adults: a randomized, placebo-controlled, double-blind phase 1 study. *Nat Med* 2021; **27**(6): 1062-70.
31. Meng FY, Gao F, Jia SY, et al. Safety and immunogenicity of a recombinant COVID-19 vaccine (Sf9 cells) in healthy population aged 18 years or older: two single-center, randomised, double-blind, placebo-controlled, phase 1 and phase 2 trials. *Signal Transduct Target Ther* 2021; **6**(1): 271.
32. Momin T, Kansagra K, Patel H, et al. Safety and Immunogenicity of a DNA SARS-CoV-2 vaccine (ZyCoV-D): Results of an open-label, non-randomized phase I part of phase I/II

clinical study by intradermal route in healthy subjects in India. *EClinicalMedicine* 2021; **38**: 101020.
33. Mulligan MJ, Lyke KE, Kitchin N, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. *Nature* 2020; **586**(7830): 589-93.
34. Pan HX, Liu JK, Huang BY, et al. Immunogenicity and safety of a severe acute respiratory syndrome coronavirus 2 inactivated vaccine in healthy adults: randomized, double-blind, and placebo-controlled phase 1 and phase 2 clinical trials. *Chin Med J (Engl)* 2021; **134**(11): 1289-98.
35. Richmond P, Hatchuel L, Dong M, et al. Safety and immunogenicity of S-Trimer (SCB-2019), a protein subunit vaccine candidate for COVID-19 in healthy adults: a phase 1, randomised, double-blind, placebo-controlled trial. *Lancet* 2021; **397**(10275): 682-94.
36. Sadoff J, Le Gars M, Shukarev G, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. *N Engl J Med* 2021; **384**(19): 1824-35.
37. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and T(H)1 T cell responses. *Nature* 2020; **586**(7830): 594-9.
38. Shu YJ, He JF, Pei RJ, et al. Immunogenicity and safety of a recombinant fusion protein vaccine (V-01) against coronavirus disease 2019 in healthy adults: a randomized, double-blind, placebo-controlled, phase II trial. *Chin Med J (Engl)* 2021; **134**(16): 1967-76.
39. Tebas P, Yang S, Boyer JD, et al. Safety and immunogenicity of INO-4800 DNA vaccine against SARS-CoV-2: A preliminary report of an open-label, Phase 1 clinical trial. *EClinicalMedicine* 2021; **31**: 100689.
40. Walsh EE, Frenck RW, Jr., Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *N Engl J Med* 2020; **383**(25): 2439-50.
41. Walter EB, Talaat KR, Sabharwal C, et al. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. *N Engl J Med* 2021.
42. Ward BJ, Gobeil P, Séguin A, et al. Phase 1 randomized trial of a plant-derived virus-like particle vaccine for COVID-19. *Nat Med* 2021; **27**(6): 1071-8.
43. Wu S, Huang J, Zhang Z, et al. Safety, tolerability, and immunogenicity of an aerosolised adenovirus type-5 vector-based COVID-19 vaccine (Ad5-nCoV) in adults: preliminary report of an open-label and randomised phase 1 clinical trial. *Lancet Infect Dis* 2021.
44. Wu Z, Hu Y, Xu M, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis* 2021; **21**(6): 803-12.
45. Xia S, Duan K, Zhang Y, et al. Effect of an Inactivated Vaccine Against SARS-CoV-2 on Safety and Immunogenicity Outcomes: Interim Analysis of 2 Randomized Clinical Trials. *Jama* 2020; **324**(10): 951-60.
46. Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infect Dis* 2021; **21**(1): 39-51.
47. Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated COVID-19 vaccine, BBIBP-CorV, in people younger than 18 years: a randomised, double-blind, controlled, phase 1/2 trial. *Lancet Infect Dis* 2021.
48. Yang S, Li Y, Dai L, et al. Safety and immunogenicity of a recombinant tandem-repeat dimeric RBD-based protein subunit vaccine (ZF2001) against COVID-19 in adults: two

randomised, double-blind, placebo-controlled, phase 1 and 2 trials. *Lancet Infect Dis* 2021; **21**(8): 1107-19.
49. Zhang J, Hu Z, He J, et al. Safety and immunogenicity of a recombinant interferon-armed RBD dimer vaccine (V-01) for COVID-19 in healthy adults: a randomized, double-blind, placebo-controlled, Phase I trial. *Emerg Microbes Infect* 2021; **10**(1): 1589-97.
50. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis* 2021; **21**(2): 181-92.
51. Zhu F, Jin P, Zhu T, et al. Safety and immunogenicity of a recombinant adenovirus type-5-vectored COVID-19 vaccine with a homologous prime-boost regimen in healthy participants aged 6 years and above: a randomised, double-blind, placebo-controlled, phase 2b trial. *Clin Infect Dis* 2021.
52. Zhu FC, Guan XH, Li YH, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* 2020; **396**(10249): 479-88.
53. Zhu FC, Li YH, Guan XH, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet* 2020; **395**(10240): 1845-54.
54. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for C-V. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. *N Engl J Med* 2021; **385**(2): 187-9.
55. Chemaitelly H, Yassine HM, Benslimane FM, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. *Nat Med* 2021; **27**(9): 1614-21.
56. Li XN, Huang Y, Wang W, et al. Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study. *Emerg Microbes Infect* 2021; **10**(1): 1751-9.
57. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. *N Engl J Med* 2021; **385**(7): 585-94.
58. Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. *N Engl J Med* 2021; **384**(20): 1885-98.
59. Nasreen S, Chung H, He S, et al. Effectiveness of COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe outcomes with variants of concern in Ontario. *Nat Microbiol* 2022; **7**(3): 379-85.
60. Sheikh A, McMenamin J, Taylor B, Robertson C, Public Health S, the EIIC. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet* 2021; **397**(10293): 2461-2.
61. Tang P, Hasan MR, Chemaitelly H, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. *Nat Med* 2021; **27**(12): 2136-43.
62. Shinde V, Bhikha S, Hoosain Z, et al. Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant. *N Engl J Med* 2021; **384**(20): 1899-909.
63. Tseng HF, Ackerson BK, Luo Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. *Nat Med* 2022.
64. Heath PT, Galiza EP, Baxter DN, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. *N Engl J Med* 2021.

65. Padmanabhan P, Desikan R, Dixit NM. Modeling how antibody responses may determine the efficacy of COVID-19 vaccines. *Nature Computational Science* 2022; **2**(2): 123-31.
66. Du Z, Wang L, Pandey A, et al. Modeling comparative cost-effectiveness of SARS-CoV-2 vaccine dose fractionation in India. *Nat Med* 2022.
67. Nishiura H, Ito K, Anzai A, Kobayashi T, Piantham C, Rodriguez-Morales AJ. Relative Reproduction Number of SARS-CoV-2 Omicron (B.1.1.529) Compared with Delta Variant in South Africa. *J Clin Med* 2021; **11**(1).
68. Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell* 2021; **184**(4): 861-80.
69. Rydyznski Moderbacher C, Ramirez SI, Dan JM, et al. Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. *Cell* 2020; **183**(4): 996-1012 e19.
70. Ward H, Whitaker M, Flower B, et al. Population antibody responses following COVID-19 vaccination in 212,102 individuals. *Nat Commun* 2022; **13**(1): 907.
71. Abu-Raddad LJ, Chemaitelly H, Bertollini R, National Study Group for C-V. Waning mRNA-1273 Vaccine Effectiveness against SARS-CoV-2 Infection in Qatar. *N Engl J Med* 2022.
72. Peng Q, Zhou R, Wang Y, et al. Waning immune responses against SARS-CoV-2 variants of concern among vaccinees in Hong Kong. *eBioMedicine* 2022; **77**.

Figure legends

Figure 1. Pooled risk ratio (in log scale) of seroconversion between fractional and standard dose group of COVID-19 vaccines. Number of seroconversion individuals and sample sizes were shown for the standard and nonstandard group, respectively.

Figure 2. Dose-response relationship of neutralizing antibodies (nAbs) and vaccine efficacy (VE) against ancestral strains induced by COVID-19 vaccines. A 2-dose schedule was assumed for RNA, protein subunit and inactivated vaccines, while 1-dose schedule was assumed for non-replicating viral vector (as suggested by the included trials). (A) Dose-response relationship of nAbs against ancestral strains. nAbs were standardized as the ratio to the convalescent sera. Dashed horizontal line indicates the average level of nAbs against ancestral strains in convalescent sera. (B) Dose-response relationship of predicted vaccine efficacy against symptomatic infections of ancestral strains. (C) Association between reduction in vaccine efficacy and dose fractionation. Reductions in vaccine efficacy were measured as the ratio between vaccine efficacy against symptomatic infections of ancestral strains between fractional and standard dose groups.

Figure 3. Predicted vaccine efficacy against SARS-CoV-2 variants of concern after fully vaccinated with half-dose vaccines. Vaccine efficacy against symptomatic infections after full vaccinations (i.e., one dose non-replicating viral vector and two doses for the rest) of half-dose are shown, with the complete dose-dependent effectiveness are shown in Supplementary Figure 8. A-E for Alpha, Beta, Gamma, Delta, and Omicron.

Figure 4. Comparison of T-cell responses against the ancestral strains elicited by dose fractioning of COVID-19 vaccines. Size of dots represent the total sample sizes of the standard and non-standard dose groups. (A) Compared to pre-vaccination. If the mean and 95% CI of the difference in mean T-cell levels before and after the fractional doses were all greater than 0, we determined T-cell responses were significantly higher between the groups. (B) Compared to people who received standard doses. If the mean and 95% CI of the difference in mean T-cell levels between the fractional and standard dose groups were all greater or less than 0, we determined T-cell responses were significantly higher or lower than that elicited by the standard dose.

Figures

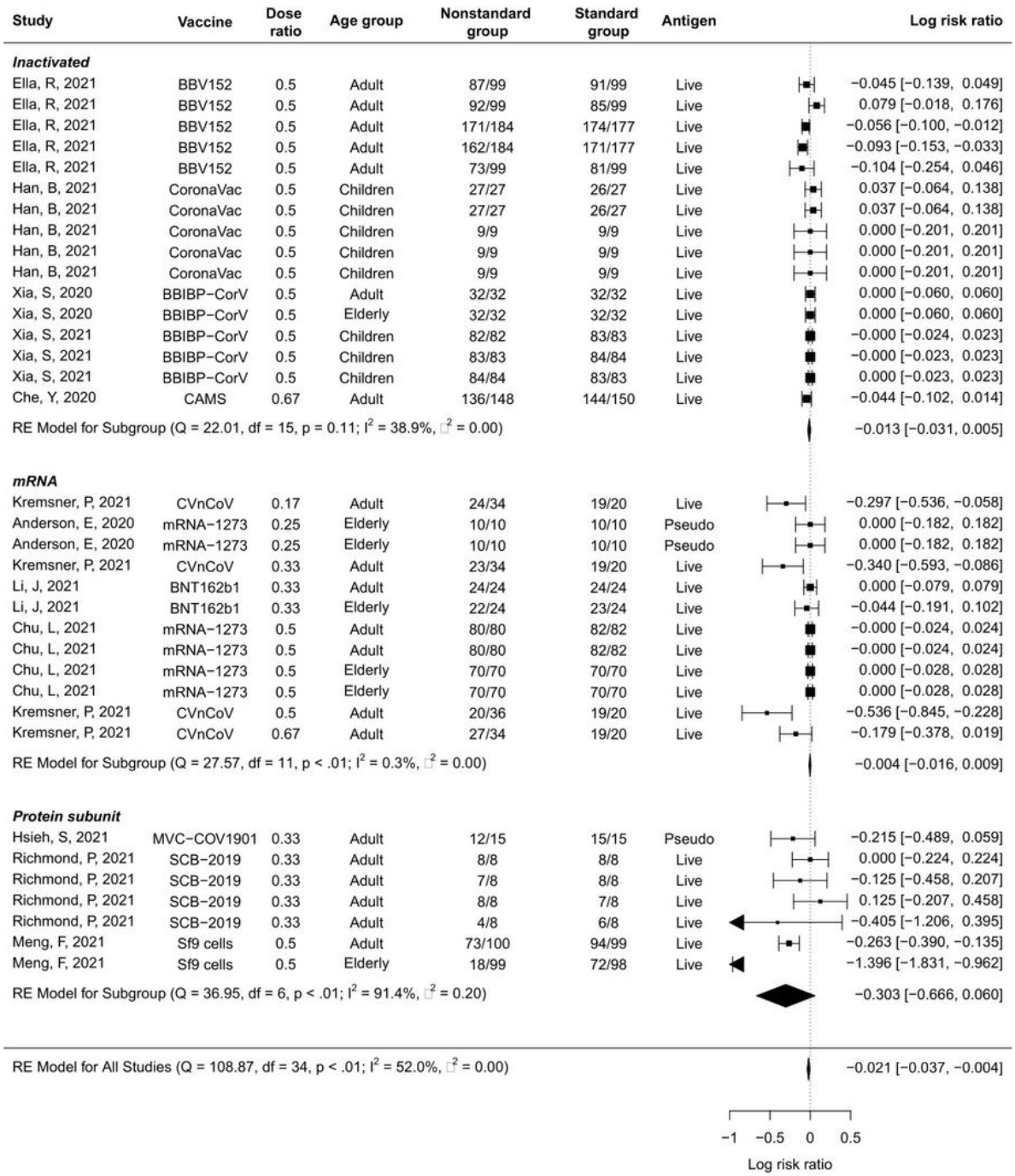

Figure 1

Pooled risk ratio (in log scale) of seroconversion between fractional and standard dose group of COVID-19 vaccines. Number of seroconversion individuals and sample sizes were shown for the standard and nonstandard group, respectively.

Figure 2

Figure 2. Dose-response relationship of neutralizing antibodies (nAbs) and vaccine efficacy (VE) against ancestral strains induced by COVID-19 vaccines. A 2-dose schedule was assumed for RNA, protein subunit and inactivated vaccines, while 1-dose schedule was assumed for non-replicating viral vector (as suggested by the included trials). (A) Dose-response relationship of nAbs against ancestral strains. nAbs were standardized as the ratio to the convalescent sera. Dashed horizontal line indicates the average level of nAbs against ancestral strains in convalescent sera. (B) Dose-response relationship of predicted vaccine efficacy against symptomatic infections of ancestral strains. (C) Association between reduction in vaccine efficacy and dose fractionation. Reductions in vaccine efficacy were measured as the ratio between vaccine efficacy against symptomatic infections of ancestral strains between fractional and standard dose groups.

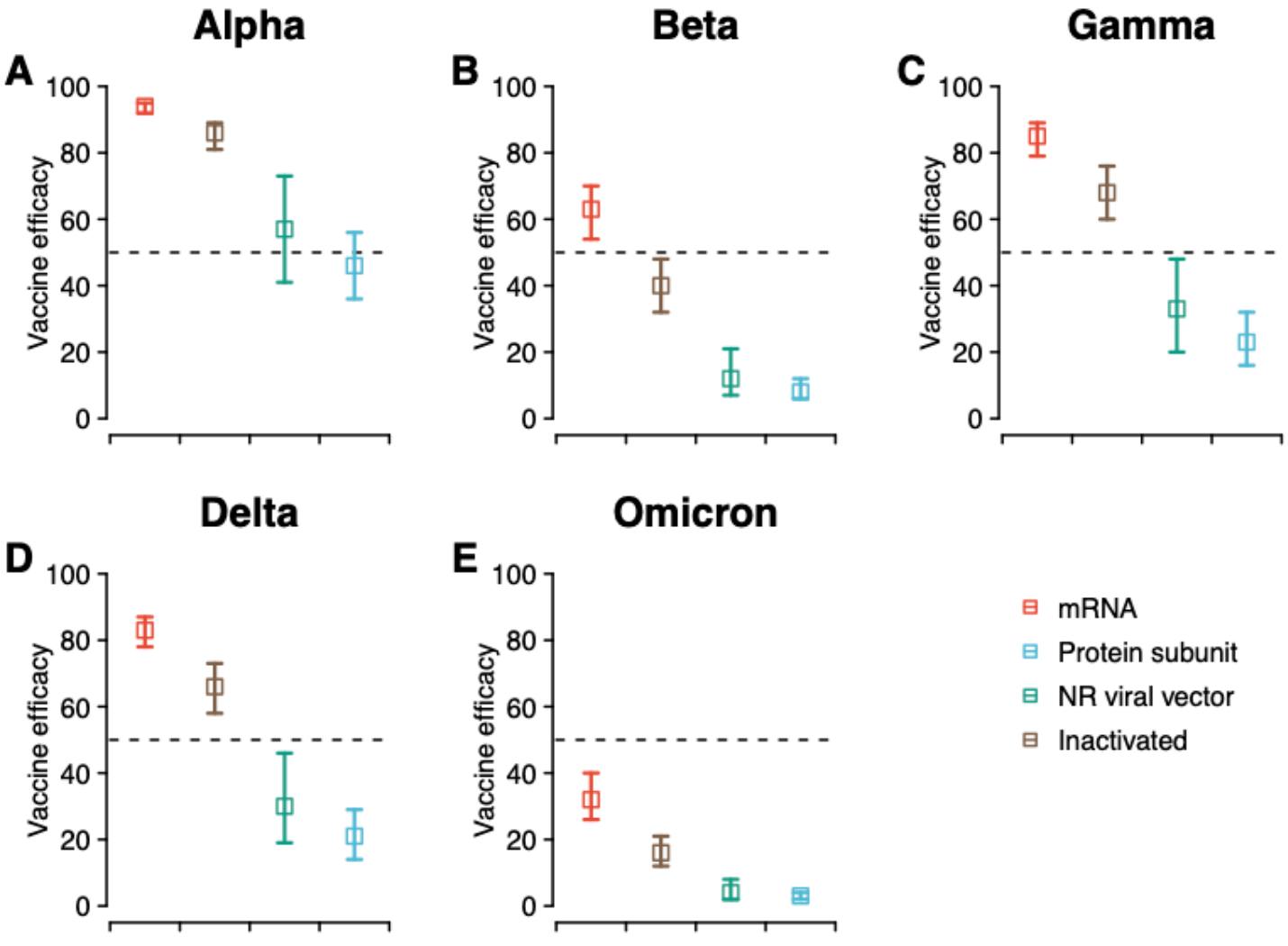

Figure 3

Figure 3. Predicted vaccine efficacy against SARS-CoV-2 variants of concern after fully vaccinated with half-dose vaccines. Vaccine efficacy against symptomatic infections after full vaccinations (i.e., one dose non-replicating viral vector and two doses for the rest) of half-dose are shown, with the complete dose-dependent effectiveness are shown in Supplementary Figure 8. A-E for Alpha, Beta, Gamma, Delta, and Omicron.

Figure 4

Figure 4. Comparison of T-cell responses against the ancestral strains elicited by dose fractioning of COVID-19 vaccines. Size of dots represent the total sample sizes of the standard and non-standard dose groups. (A) Compared to pre-vaccination. If the mean and 95% CI of the difference in mean T-cell levels before and after the fractional doses were all greater than 0, we determined T-cell responses were significantly higher between the groups. (B) Compared to people who received standard doses. If the mean and 95% CI of the difference in mean T-cell levels between the fractional and standard dose groups were all greater or less than 0, we determined T-cell responses were significantly higher or lower than that elicited by the standard dose.

Supplementary Files

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

- Supplementary.docx