Dear Editor-in-Chief,

Please find enclosed the revised version of our manuscript titled "Efficacy and Safety of an Inactivated Virus-Particle Vaccine for SARS-CoV-2, BIV1-CovIran: Findings from a Randomised, Placebo-Controlled, Double-Blind, Multicenter Phase III Clinical Trial amid the Delta Variant Peak", which we would like to submit for publication as an original article in The BMJ.

Please find enclosed our reply to the comments of the editorial committee, the statistical editor, the research editors, and the two reviewers. We have appreciated the encouraging, fair, and constructive comments, and have provided a highlighted version of the revised manuscript. The manuscript has undergone extensive revision. The manuscript reporting the results of the phase I and phase II clinical trials has been published in BMJ Open, which is now cited wherever necessary in the revised manuscript. The trial registration, the study protocol, and the manuscript have also been thoroughly reviewed for any conflicts, and corresponding explanations have been provided. Initially, the study protocol was submitted to another journal; however, we did not expect such a protracted review and decision process. Now that we are preparing the point-by-point response to the editorial committee, the statistical editor, research editors, and the two reviewers at The BMJ, the journal has still not decided on the study protocol, although we have provided point-by-point responses to the reviewers. Thus, we have asked the journal to discontinue the manuscript consideration. Upon resubmission, we are submitting the study protocol as a supplement (supplemental appendix 1) for your kind consideration.

We feel that the changes made according to the comments have improved the quality of the manuscript, and we would be happy, if it now meets the criteria for publication in The BMJ.

Best regards,

Sincerely,

Mohammadreza Salehi, MD

Affiliation: Department of Infectious Diseases and Tropical Medicine, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

Email: salehi.mohamad3@gmail.com; mr-salehi@sina.tums.ac.ir

**Editorial Committee Evaluation**

Editors felt that your paper covered a timely and important research question. However, there are several issues that need to be clarified before we can make a final decision - in particular, the results of the phase I and II trials, and an explanation for discrepancies between the trial registration, protocol, and manuscript. All of the queries from editors are listed below.

**Authors**

The authors would like express their most sincere words of appreciation for the time and the consideration of the editorial committee at The BMJ. We have thoroughly gone through the comments of the editorial committee, the statistical editor, the research editors, and the two reviewers. The manuscript has undergone extensive revision. The manuscript reporting the results of the phase I and phase II clinical trials has been published in BMJ Open, which is now cited wherever necessary in the revised manuscript. The trial registration, the study protocol, and the manuscript have also been thoroughly reviewed for any conflicts, and corresponding explanations have been provided. Initially, the study protocol was submitted to another journal; however, we did not expect such a protracted review and decision process. Now that we are preparing the point-by-point response to the editorial committee, the statistical editor, research editors, and the two reviewers at The BMJ, the journal has still not decided on the study protocol, although we have provided point-by-point responses to the reviewers. Thus, we have asked the journal to discontinue the manuscript consideration. Upon resubmission, we are submitting the study protocol as a supplement for your kind consideration at The BMJ.

**Statistical editor**

1. Some queries from reviewers re blinding, generation of random allocation sequence, allocation concealment. Cheung notes a problem with efficacy analysis. These will all need to be addressed.

**Authors**

Thank you for your time and efforts regarding this manuscript. While addressing the comments of Fengcai Zhu, we provided more details about re-blinding, generation of random allocation sequence, and allocation concealment in the methods section of the manuscript. The paragraphs now read:

Sample Size

The sample size was calculated based on the WHO recommendation of achieving 150 cases across the vaccine/placebo groups, with an ultimate efficacy of 60% (lower bound of 30%). Estimating the COVID-19 incidence rate of 1% among the unimmunised population in Iran and a 10% dropout rate, a total of 20,000 participants was required. The number of participants in each city was cardinally determined commensurate with the city population, where each trial site was located. To match the study population's age distribution to the age pyramid of the country [1], 20% of the study population in each city included participants aged 51-75 years. Participants were randomly assigned to the intervention/placebo groups within each city with a ratio of 2:1, respectively.

**Randomisation and Enrollment**

Using an electronic tool [2], the randomisation sheet subsuming block sequences of 3 and 6 was produced. A unique four-character randomisation code was generated upon enrollment of each eligible participant using the electronic tool [12]. Then, four other letters were added to the randomisation code: the first two letters of the participant's first name and the first two letters of their last name to form the participant's unique code. During the trial, all procedures were performed using the participant's unique code, and the identification information remained confidential by the principal investigator.

**Concealment and Blinding**

Vaccine and placebo vials were manufactured with the same appearance, label, and participant unique code, to ensure the blindness of participants, researchers, and outcome assessors. After the vaccine or placebo administration, the participant's unique code and administration date were written on the outer packaging box, and the label was recorded on the randomisation sheet. The study personnel checked all the information before vaccine/placebo administration. During the study, all packages were archived and maintained. In cases of any emergency events, including serious AEs, the query of emergency decoding and unblinding would urgently be requested by the principal investigator.

As for the comment on the efficacy analysis, the follow-up duration was 90 days (from day 42 to day 132, the first injection of vaccine/placebo occurring on day zero). Thus, each participant at most could contribute 90/365=0.246 person-year. The median days of time-to-event in this study were 83 days (minimum=42, maximum=131), counting from the first day of the trial. We acknowledge that the manuscript text was equivocal in this sense, and it could be interpreted that the follow-up period was 90-14=76 days. Thus, we revised the manuscript to enhance clarity in this sense. The corresponding sentences now read:

**Abstract, Main outcome measures:**

The vaccine efficacy for a 90-day follow-up period; safety, and explanatory immunogenicity assessment; variant detection during the trial.

**Introduction (objective):**

Here, we report efficacy, safety, and exploratory immunogenicity findings from a multicenter randomised placebo-controlled Phase III clinical trial evaluating two 5µg shots of BIV1-CovIran vaccine with a 28-day interval and a 90-day follow-up after the second injection, with the participation of 20,000 individuals aged 18-75 years. Given that the delta variant was initially reported in Iran on June 8, 2021 [3], which overlapped with this Phase III clinical trial, the results could also shed light on the vaccine efficacy on this variant.

**Methods, Overview:**

This randomised, placebo-controlled, double-blind, multicenter Phase III clinical trial was conducted to investigate the efficacy (90-day follow-up) and safety of an inactivated whole virus particle vaccine, BIV1-CovIran, among 20,000 participants aged 18-75 years located in six cities of Iran.

**Methods, Study Endpoints, Efficacy Endpoints**

The efficacy of BIV1-CovIran was primarily assessed by the onset of definitive symptomatic COVID-19 infection during a 90-day follow-up after the second injection.

**Methods, Statistical Analysis:**

Efficacy was assessed by the onset of COVID-19 among the efficacy population who were followed for 90 days after the second dose. The maximum contribution of each participant to person-time equalled 0.246 (90/365) person-years.

**Discussion, the first paragraph:**

This study presents the findings from the phase III clinical trial of BIV1-CovIran, an inactivated whole virus particle vaccine for SARS-CoV-2, adjuvanted with aluminium hydroxide. Vaccine efficacy was assessed during a 90-day follow-up after the second dose. Based on the final per-protocol analysis, a two-dose regimen of the vaccine (5µg per dose, given 28 days apart) was well-tolerated, induced significant seroconversion, was 50% effective against symptomatic COVID-19 and was 83% effective against critical COVID-19. Moreover, there were no deaths in the vaccine group during the follow-up period. Our preliminary vaccine efficacy against symptomatic COVID-19 infection was 50%, with a vaccine efficacy of 91% among participants aged 65-75 years.

**Statistical editor**

2. More information needed for the sample size calculation. Is the assumption a rate reduction from 1 per 100 to 0.4 per 100? On this basis would expect 67 cases in the anticipated 6650 controls and 63 amongst the 13350 receiving vaccine, which is below the 150 cases mooted. No adjustment seems to be made for within centre correlation.

**Authors**

Thank you for your meticulous comment. Kindly note that while designing the study before the emergence of the delta variant, the assumption was a COVID-19 incidence rate of 1% per month among the unimmunised population in Iran and a 10% dropout rate, which yielded a sample size of 20,000 participants. We double-checked the methods and realised that this had not been presented correctly, for which we apologise. The corresponding sentence now reads:

Estimating the COVID-19 incidence rate of 1% per month among the unimmunised population in Iran and a 10% dropout rate, a total of 20,000 participants was required.

While addressing the reviewers' comments, we also highlighted the follow-up period of this study, which was 90 days (median=83).

**Statistical editor**

3. Participants were volunteers answering calls on mass and social media platforms. What bias might be expected in such a volunteer group and how might this impact generalisability?
Internet penetration rate

**Authors**

Thank you for your meticulous comment. We understand the concern of the statistical editor. Kindly note that at the recruiting phase of this trial, less than 3% of the Iranian population had been fully vaccinated for COVID-19 [4]. Thus, some people would be eager to participate in a domestic COVID-19 vaccine trial and would follow the news on mass and social media. Considering that the internet penetration rate exceeds 84% in Iran [5], the study volunteers would include a wide range of people, which could in turn decrease the selection bias.

**Statistical editor**

4. The 400 participants for the explanatory immunogenicity assessment were a convenience sample from here and more information of that selection process might be helpful.

**Authors**

Thank you for your comment. Kindly note that Tehran, the main trial site with 43.6% of participants, was chose for explanatory immunogenicity assessment. We revised the corresponding paragraph in the methods section, which now reads:

To further evaluate the immunogenicity enhancement of the BIV1-CovIran vaccine among Phase III participants, the humeral response against SARS-CoV-2 in a subsample of 400 participants located in Tehran was assessed using the convenience sampling method. We evaluate the geometric mean titers (GMT), geometric mean ratios (GMR) of antibodies against SARS-CoV-2 and the seroconversion rates 14 days after the second injection. The blood samples were collected from the participants before the first injection and on day 14 after the second injection. Neutralising, anti-receptor binding domain (RBD), and anti-spike glycoprotein antibodies were measured using Enzyme-linked Immunosorbent Assay (ELISA) kits [8]. Seroconversion was defined as a post-vaccination IgG titer that was at least four-fold higher than the baseline titer.

**Statistical editor**

5.How many missing values were there and in which variables? Imputation should be considered.

**Authors**

Thank you for your meticulous comment. As many as 20,000 participants, 13,335 (66.7%) in the intervention and 6,665 (33.3%) in the placebo group, were included in the study. After the exclusion of the participants who had not promptly received two doses of vaccine/placebo, were lost to follow-up, passed away, or withdrew from the study were not included in the efficacy analysis. The efficacy analysis was conducted with the participation of 19401 individuals: 6,456 in the placebo and 12,945 in the intervention group. The reasons for participants' exclusion at each step are presented in Figure 2.

**Statistical editor**

6. There were 164 serious AEs with 51.8% (85) in the intervention group. Since there were double the number of individuals in the intervention group this suggest quite a substantial reduction in rate of serious AEs. Is there an explanation for this?

**Authors**

Thank you for your meticulous comment. We agree with the statistical editor; thus, we double-checked Table S3. Serious AEs in this study were defined as death, life-threatening events, hospitalisation due to any cause, prolonged hospitalisation period, and any other conditions deemed serious by the principal investigator. As presented in Table S3, 100 of 164 serious AEs were hospitalisations due to COVID-19: 53 in the placebo group and 47 in the intervention group. The way we see it, a potential explanation for this observation could be the partial protection against COVID-19 hospitalisation among participants who received the vaccine.

**Research editors**

1. The protocol and phase I and II results all need to be carefully reviewed. Have they phase I and II results been published? It would be helpful to summarise the safety and immunogenecity results from the phase I and II in this paper?

**Authors**

The authors would like to express their most sincere words of appreciation for the research editors' time and consideration. The manuscript reporting the results of the phase I and phase II clinical trials has been published in BMJ Open, which is now cited wherever necessary in the revised manuscript. Initially, the study protocol was submitted to another journal; however, we did not expect such a protracted review and decision process. Now that we are preparing the point-by-point response to the editorial committee, the statistical editor, research editors, and the two reviewers at The BMJ, the journal has still not decided on the study protocol, although we have provided point-by-point responses to the reviewers. Thus, we have asked the journal to discontinue the manuscript consideration. Upon resubmission, we are submitting the study protocol as a supplement for your kind consideration at The BMJ. We also revised the last paragraph of the introduction and provided more details regarding phase I and phase II trials. The paragraph now reads:

We previously reported phase I and Phase II safety and immunogenicity results from clinical trials of the BIV1-CovIran vaccine [4], an inactivated whole virus particle vaccine [6]. Following the administration of the two shots of 5µg dose of BIV1-CovIran vaccine with a 28-day interval, the were no vaccine-related severe adverse events (AEs). Moreover, the vaccine significantly enhanced the immunity of all vaccine recipients against SARS-CoV-2. In phase II, the seroconversion rate of neutralising-antibody was 82.8% two weeks after the second dose [4]. These findings supported the progression of the BIV1-CovIran vaccine into Phase III. Here, we report efficacy, safety, and exploratory immunogenicity findings from a multicenter randomised placebo-controlled Phase III clinical trial evaluating two 5µg shots of BIV1-CovIran vaccine with a 28-day interval and a follow-up period of at least 14 days after the second injection with the participation of 20,000 individuals aged 18-75 years. Given that the delta variant was initially reported in Iran on June 8, 2021 [3], which overlapped with this Phase III clinical trial, the results could also shed light on the vaccine efficacy on this variant.

**Research editors**

2. The published protocol was referred to a couple of times in the paper but there's no reference, nor did I find the report of the phase I/II trial - is this still under review in BMJ Open?

**Authors**

Thank you for your meticulous comment. The manuscript reporting the results of the phase I and phase II clinical trials has been published in BMJ Open, which is now cited wherever necessary in the revised manuscript. Initially, the study protocol was submitted to another journal; however, we did not expect such a protracted review and decision process. Thus, we have asked the journal to discontinue the manuscript consideration. Upon resubmission, we are submitting the study protocol as a supplement for your kind consideration at The BMJ.

**Research editors**

3. The Phase I/II clinical paper under review at BMJ Open should be shared with us as we evaluate this paper and, ideally, should be posted to medRxiv so others have access to it. As should the protocol paper for this trial that is under review at Frontiers in Medicine. I only found the pre-clinical paper on bioRxiv.

**Authors**

Thank you for your meticulous comment. The manuscript reporting the results of the phase I and phase II clinical trials have been published in BMJ Open, which is now cited wherever necessary in the revised manuscript. Initially, the study protocol was submitted to another journal; however, we did not expect such a protracted review and decision process. Thus, we have asked the journal to discontinue the manuscript consideration. Upon resubmission, we are submitting the study protocol as a supplement for your kind consideration at The BMJ.

**Research editors**

4. The primary efficacy outcomes in registry are "Vaccine efficacy" and "Severe COVID-19 cases" 14-180d after second dose, while in the paper, it is "Vaccine efficacy (onset of symptomatic cases)"

14-90d after second dose. And there are some important differences in secondary outcomes between paper and registry (e.g.Vaccine efficacy 181-360d after second dose in registry, etc)

**Authors**

Thank you for your meticulous comment. Kindly note that the phase III trial was designed to follow participants for safety and efficacy for 365 days after the second dose. However, ethical considerations prevented following placebo recipients for 365 days without active immunisation. Once approved vaccines for COVID-19 were publically available, the national ethical committee required all clinical trials for COVID-19 vaccines to decode their data and notify participants in the placebo group to get vaccinated for COVID-19, after three months of the second placebo administration. Subsequently, participants in the placebo group administered the currently available COVID-19 vaccines. We initially aimed to present the interim analysis based on the 180-days follow-up, as stated in the study protocol. After the request of the ethical committee, we provided the interim report for the Iranian Food and Drug Administration based on a shorter follow-up period (median= 83 days) after the second dose, the results of which are presented in the current study. The follow-up duration of other COVID-19 vaccine phase III trials after the second dose was 99 days (median) for BBV152 [7], 112 days (median) for BBIBP-CorV [8], 61 days (median) for ChAdOx1 nCoV-19 [9], 2 months (median) for ChAdOx1 nCoV-19 [10], six months for BNT162b2 [11]. Moreover, this was 90 days after the first dose for CoronaVac [12].

We have included these details in the strengths and limitations section of the manuscript, which reads: The phase III trial was designed to follow participants for safety and efficacy for 365 days after the second dose. However, ethical considerations prevented following placebo recipients for 365 days without active immunisation. Once approved vaccines for COVID-19 were publically available, the national ethical committee required all clinical trials for COVID-19 vaccines to decode their data and notify participants in the placebo group to get vaccinated for COVID-19 after three months of the second placebo administration. Subsequently, participants in the placebo group administered the currently available COVID-19 vaccines. We initially aimed to present the interim analysis based on the 180-days follow-up, as stated in the study protocol. After the request of the ethical committee, we provided the interim report for the Iranian Food and Drug Administration based on a shorter follow-up period (median= 83 days) after the second dose, the results of which are presented in the current study. The follow-up duration of other COVID-19 vaccine phase III trials after the second dose was 99 days (median) for BBV152 [7], 112 days (median) for BBIBP-CorV [8], 61 days (median) for ChAdOx1 nCoV-19 [9], 2 months (median) for ChAdOx1 nCoV-19 [10], six months for BNT162b2 [11]. Moreover this was 90 days after the first dose for CoronaVac [12].

**Research editors**

5. Reporting of outcomes (paper vs. protocol vs. registry) need reconciliation

**Authors**

Thank you for your meticulous comment. As presented in the study protocol, the phase III trial was designed to follow participants for safety and efficacy for 365 days after the second dose. However, ethical considerations prevented following placebo recipients for 365 days without active immunisation. Once approved vaccines for COVID-19 were publically available, the national ethical committee required all clinical trials for COVID-19 vaccines to decode their data and notify participants in the placebo group to get vaccinated for COVID-19, after three months of the second placebo administration. Subsequently, participants in the placebo group administered the currently available COVID-19 vaccines. We initially aimed to present the interim analysis based on the 180-days follow-up, as stated in the study protocol. After the request of the ethical committee, we provided the interim report for the Iranian Food and Drug Administration based on a shorter follow-up period (median= 83 days) after the second dose, the results of which are presented in the current study.

**Research editors**

6. Outcome ascertainment. Please can authors clarify: How did they assess `definitive symptomatic COVID-19 infection"?

**Authors**

Thank you for your comment. During the trial, upon the report of any suspicious COVID-19 symptoms, a nasopharyngeal specimen would be obtained at the clinical trial site, and RT-PCR would be performed at a central laboratory. In cases of negative RT-PCR tests, participants underwent

further RT-PCR tests after 48 hours unless their symptoms regressed. Positive RT-PCR tests would indicate definitive symptomatic COVID-19. The corresponding sentences in the assessments section of the methods were revised to enhance clarity and now read:
Upon the report of any suspicious COVID-19 symptoms, a nasopharyngeal specimen would be obtained at the clinical trial site, and RT-PCR would be performed at a central laboratory. In cases of negative RT-PCR tests, participants underwent further RT-PCR tests after 48 hours unless their symptoms regressed. Positive RT-PCR tests would indicate definitive symptomatic COVID-19.

**Research editors**

How was "severe and critical COVID-19 among participants" defined ? How did they assess whether participants had symptoms (did they get telephone prompts, or something else ?), and how many were lost to FU?

**Authors**

Thank you for your comment. Kindly note that COVID-19 severity status was categorised as symptomatic non-severe, severe, and critical based on the diagnosis scheme from the WHO [13] (supplemental appendix 1). We also included this detail in the assessment section of the methods, which now reads:
In phase III, participants were undergone face-to-face interviews in the screening session, first injection day, and second injection day. In addition, over-the-telephone follow-up visits were held on a 14-day interval following the injection. A reactogenicity diary book was allocated to participants regarding any possible COVID-19 symptoms. All Phase III participants would contact 24/7 study call centres, providing video call or file-sharing features, should they have any concerns or need medical attention using a mobile application designed for this clinical trial. Suspected COVID-19 cases were defined if participants presented (1) at least two of the following symptoms lasting for at least 48 hours: fever (axillary temperature ≥37.5°C), chills, sore throat, stuffy nose, myalgia, fatigue, headache, nausea or vomiting, or diarrhoea or (2) at least one respiratory sign or symptom (including cough, shortness of breath), new olfactory or taste disorder, or radiographic evidence of COVID-19–like pneumonia. Upon the report of any suspicious COVID-19 symptoms, a nasopharyngeal specimen would be obtained at the clinical trial site, and RT-PCR would be performed at a central laboratory. In cases of negative RT-PCR tests, participants underwent further RT-PCR tests after 48 hours unless their symptoms regressed. Positive RT-PCR tests would indicate definitive symptomatic COVID-19. COVID-19 severity status was categorised as symptomatic non-severe, severe, and critical based on the diagnosis scheme from the WHO [13] (supplemental appendix 1).

Regarding the missing data, as many as 20,000 participants, 13,335 (66.7%) in the intervention and 6,665 (33.3%) in the placebo group, were included in the study. After the exclusion of the participants who had not promptly received two doses of vaccine/placebo, were lost to follow-up, passed away, or withdrew from the study were not included in the efficacy analysis. The efficacy analysis was conducted with the participation of 19401 individuals: 6,456 in the placebo and 12,945 in the intervention group. The reasons for participants' exclusion at each step are presented in Figure 2.

**Research editors**

7. Should seropositive participants at baseline (n=6458) be included in the efficacy analysis at all?

**Authors**

Thank you for your meticulous comment. As presented in efficacy endpoints in the methods section, the efficacy of BIV1-CovIran was primarily assessed by the onset of definitive symptomatic COVID-19 infection during a 90-day follow-up after the second injection. The onset of severe and critical COVID-19 among participants of Phase III and deaths due to COVID-19 during 90 days after the second dose injection was assessed as the secondary efficacy endpoints. In addition, we evaluated the post hoc efficacy of the BIV1-CovIran vaccine for COVID-19 symptomatic cases, hospitalisation and death by subgroups, including sex, age, serology, and location.
Accordingly, we reported the vaccine efficacy among the efficacy population as the primary end point in the main manuscript and Table 3. Moreover, post hoc analysis for vaccine efficacy was presented in the main text and Table S1. This approach to reporting the results was commensurate with the phase III clinical trial reports of BNT162b2 [11] and BBIBP-CorV [14]

**Research editors**

8. Can the authors provide more information on the 44,049 excluded patients

**Authors**

Thank you for your comment. Figure 1 (Figure 2 in the revised version) was revised, and more details were provided.

**Research editors**

9. The incidence of symptomatic Covid was 10 times of what's expected (1446 cases vs expected 150 cases and 10.6% in the control group infected vs 1% (expected from "unimmunised population in Iran"). Can the authors explain why?

**Authors**

We agree with the meticulous comment of the research editors. While designing this phase III trial, we calculated the sample size based on the available data on the dominant SARS-CoV-2 variants at the time, being the alpha and beta variants [15]. In our opinion, this phase III trial coincided with the delta variant surge, the $R_0$ of which was much higher than the ancestral variants [16]. Thus, the incidence of symptomatic COVID-19 during the trial was beyond our initial expectations.

**Research editors**

10. Please check the vaccine efficacy calculation. The RR of symptomatic infection of vaccinated vs control groups seemed to be 0.55 (758/12942 in intervention group and 688/6462 in the unvaccinated group), thus we wondered if the vaccine efficacy should be 0.45? (though we may be wrong)

**Authors**

Thank you for your comment. Kindly note that vaccine efficacy was calculated using a Poisson regression compared to the placebo group, defining the dependent variable as the number of incident cases, the independent variable as the treatment group, and the offset as the person-years. Efficacy analysis was performed on the efficacy population, who were fully vaccinated and had a vaccine/placebo administration interval of 28 ±3 days. Efficacy was assessed by the onset of COVID-19 among the efficacy population who were followed for 90 days after the second dose. The maximum contribution of each participant to person-time equalled 0.246 (90/365) person-years. Simultaneously, the vaccine efficacy against severe and critical cases of COVID-19 and deaths due to COVID-19 was analysed. Considering the study population size during this Phase III clinical trial, it was assumed that missing covariates at baseline would not significantly affect the vaccine efficacy calculation and were not imputed [17].

$$Vaccine\ efficacy\ (\%) = \left(1 - \frac{\text{Incidence density of intervention group}}{Incidence\ density\ of\ placebo\ group}\right) \times 100$$

$$Incidence\ density = \left(\frac{\#\ confirmed\ cases\ during\ the\ effective\ follow-up}{\#observation\ years\ of\ all\ vaccinated\ participants}\right) \times 100$$

**Research editors**

11. Was the efficacy analysis conducted among the compliers? It may be helpful to make this clearer in the manuscript

**Authors**

Thank you for your comment. We reviewed the methods section and revised the statistical analysis for enhanced clarity, which now reads:

Efficacy analysis was performed on the efficacy population, who were fully vaccinated and had a vaccine/placebo administration interval of 28 ±3 days. Efficacy was assessed by the onset of COVID-19 among the efficacy population who were followed for 90 days after the second dose.

**Research editors**

12. Is there 180 day outcome data available now that can be included

**Authors**

Thank you for your comment. The phase III trial was designed to follow participants for safety and efficacy for 365 days after the second dose. However, ethical considerations prevented following placebo recipients for 365 days without active immunisation. Once approved vaccines for COVID-19 were publically available, the national ethical committee required all clinical trials for COVID-19

vaccines to decode their data and notify participants in the placebo group to get vaccinated for COVID-19, after three months of the second placebo administration. Subsequently, participants in the placebo group administered the currently available COVID-19 vaccines. We initially aimed to present the interim analysis based on the 180-days follow-up, as stated in the study protocol. After the request of the ethical committee, we provided the interim report for the Iranian Food and Drug Administration based on a shorter follow-up period (median= 83 days) after the second dose, the results of which are presented in the current study. Please be informed that although such data were/are being gathered during the trial, the data of day 132 onwards are an amalgam of various combinations of the available COVID-19 vaccines, which precludes us from assessing any of the study end points.

**Research editors**

13. Can you place these results in the context of other vaccines? And in the context of current variants (e.g. Omicron) and vaccine strategies (e.g. boosters)

**Authors**

Thank you for your comment. We reviewed the discussion and included the following paragraph, which we hope addresses the comment:

Initially reported in late 2021, the highly contagious B.1.1.529 (Omicron) variant of concern has globally outcompeted the earlier variants with its higher rates of spike protein mutation, resulting in higher immune evasion capacity [18,19]. The Omicron variant has reportedly challenged the effectiveness and neutralisation capacity of SARS-CoV-2 vaccines, developed initially against the Wuhan variant [18,20–23]. Among the potential mitigating strategies for Omicron or future variants of concern, choosing between delivering booster doses of conventional COVID-19 vaccines, homologous or heterologous [24], and developing Omicron-based vaccine boosters [25] is an ongoing debate which needs extensive investigation in the future studies.

**Reviewer 1**

Yin Bun Cheung, Duke-NUS Medical School

**Reviewer**

1. Efficacy against symptomatic Covid-19 should be included in the Conclusion statement in the Abstract.

**Authors**

The authors would like to express their most sincere appreciation for your time and consideration. The comment was addressed accordingly, and the conclusion now reads:

A two-dose regimen of BIV1-CovIran vaccine conferred 50.2%, 70.5% and 83.1% efficacy against symptomatic, severe and critical COVID-19. Vaccination was well tolerated, with no safety concerns raised.

**Reviewer**

2. The follow-up was only up to 90 days post dose 2. Since vaccine efficacy tends to wane over time, the estimates of efficacy would likely drop if the trial had a longer follow-up time. This should be acknowledged. To put things into perspective, it is helpful to include a brief review/comment on the follow-up duration of other Covid-19 vaccine trials.

**Authors**

We agree with the reviewers' comments. Kindly note that ethical considerations prevented following placebo recipients for 365 days without active immunisation once approved vaccines for COVID-19 were available for participants. As requested by the ethical committee, the data were decoded and participants in the placebo group were notified to get vaccinated for COVID-19. Subsequently, participants in the placebo group administered the currently available COVID-19 vaccines. We initially aimed to present the interim analysis based on the 180-days follow-up, as stated in the study protocol. After the request of the ethical committee, we requested an amendment to the study protocol to investigate the vaccine efficacy based on a shorter follow-up period (median= 83 days) after the second dose, the results of which are presented in the current study. The follow-up duration of other COVID-19 vaccine phase III trials after the second dose was 99 days (median) for BBV152 [7], 112 days (median) for BBIBP-CorV [8], 61 days (median) for ChAdOx1 nCoV-19 [9], 2 months (median) for ChAdOx1 nCoV-19 [10], six months for BNT162b2 [11]. Moreover this was 90 days after the first dose for CoronaVac [12]. Accordingly, this was addressed in the Strengths and limitations section of the manuscript, which now reads:

The phase III trial was designed to follow participants for safety and efficacy for 365 days after the second dose (supplemental appendix 1). However, ethical considerations prevented following placebo recipients for 365 days without active immunisation. Once approved vaccines for COVID-19 were publically available, the national ethical committee required all clinical trials for COVID-19 vaccines to decode their data and notify participants in the placebo group to get vaccinated for COVID-19, after three months of the second placebo administration. Subsequently, participants in the placebo group were administered the currently available COVID-19 vaccines. We initially aimed to present the interim analysis based on the 180-days follow-up, as stated in the study protocol. After the request of the ethical committee, we provided the interim report for the Iranian Food and Drug Administration based on a shorter follow-up period (median= 83 days) after the second dose, the results of which are presented in the current study. The follow-up duration of other COVID-19 vaccine phase III trials after the second dose was 99 days (median) for BBV152 [7], 112 days (median) for BBIBP-CorV [8], 61 days (median) for ChAdOx1 nCoV-19 [9], 2 months (median) for ChAdOx1 nCoV-19 [10], six months for BNT162b2 [11]. Moreover, this was 90 days after the first dose for CoronaVac [12].

**Reviewer**

3. The analysis seems to be wrong: Efficacy was evaluated from 14 to 90 days post dose 2. Therefore, each participant at most can contribute 0.211 person-year. But the person-years shown in Table 3 are larger than the number of participants multiplied by 0.211. The discrepancy seems too large to be explained by rounding.

**Authors**

Thank you for your meticulous comment. In our efficacy analysis, the follow-up duration was 90 days (from day 42 to day 132, the first injection of vaccine/placebo occurring on day zero). Thus,

each particiapant at most could contribute 90/365=0.246 person-year. The median days of time-to-event in this study was 83 days (minimum=42, maximum=131), counting from the first day of the trial. We acknowledge that the manuscript text was equivocal in this sense, and it could be interpreted that the follow-up period was 90-14=76 days. Thus, we revised the manuscript to enhance clarity in this sense. The corresponding sentences now read:

**Abstract, Main outcome measures:**

The vaccine efficacy for a 90-day follow-up period; safety, and explanatory immunogenicity assessment; variant detection during the trial.

**Introduction (objective):**

Here, we report efficacy, safety, and exploratory immunogenicity findings from a multicenter randomised placebo-controlled Phase III clinical trial evaluating two 5µg shots of BIV1-CovIran vaccine with a 28-day interval and a 90-day follow-up after the second injection, with the participation of 20,000 individuals aged 18-75 years. Given that the delta variant was initially reported in Iran on June 8, 2021 [3], which overlapped with this Phase III clinical trial, the results could also shed light on the vaccine efficacy on this variant.

**Methods, Overview:**

This randomised, placebo-controlled, double-blind, multicenter Phase III clinical trial was conducted to investigate the efficacy (90-day follow-up) and safety of an inactivated whole virus particle vaccine, BIV1-CovIran, among 20,000 participants aged 18-75 years located in six cities of Iran.

**Methods, Study Endpoints, Efficacy Endpoints**

The efficacy of BIV1-CovIran was primarily assessed by the onset of definitive symptomatic COVID-19 infection during a 90-day follow-up after the second injection.

**Methods, Statistical Analysis:**

Efficacy was assessed by the onset of COVID-19 among the efficacy population who were followed for 90 days after the second dose. The maximum contribution of each participant to person-time equalled 0.246 (90/365) person-years.

**Discussion, the first paragraph:**

This study presents the findings from the Phase III clinical trial of BIV1-CovIran, an inactivated whole virus particle vaccine for SARS-CoV-2, adjuvanted with aluminium hydroxide. Vaccine efficacy was assessed during a 90-day follow-up after the second dose. Based on the final per-protocol analysis, a two-dose regimen of the vaccine (5µg per dose, given 28 days apart) was found to be well-tolerated, induce significant seroconversion, and be 50% effective against symptomatic COVID-19, 83% effective against critical COVID-19. Moreover, there were no deaths in the vaccine group during the follow-up period. Our preliminary vaccine efficacy against symptomatic COVID-19 infection was 50%, with a vaccine efficacy of 91% among participants aged 65-75 years.

While double-checking the individual-level data, we realised that the time-to-event for two participants, one in the vaccine group and one in the placebo group, exceeded 132. As we aimed to report the vaccine efficacy based on a 90-days follow-up, the two participants were not supposed to be included in the efficacy analysis. We apologise for this error and would like to thank the reviewer for his valuable comment.

**Reviewer**

Minor issues:

1. Page 9 line 10: It seems odd to state that "upon onset of suspicious Covid-19 symptoms, a nasopharyngeal specimen would be obtained". The earliest possible time of obtaining the specimen should be "upon report of suspicious Covid-19 symptoms"?

**Authors**

Thank you for your comment. The sentence was revised and now reads:

Upon the report of any suspicious COVID-19 symptoms, a nasopharyngeal specimen would be obtained at the clinical trial site, and RT-PCR would be performed at a central laboratory.

**Reviewer**

2. Page 9 line 27: Should define "definitive symptomatic Covid-19 infection" here. The Methods section has only defined "suspected Covid-19 infection".

**Authors**

Thank you for your comment. Amended. The paragraph was revised and now reads:

Suspected COVID-19 cases were defined if participants presented (1) at least two of the following symptoms lasting for at least 48 hours: fever (axillary temperature ≥37.5°C), chills, sore throat, stuffy nose, myalgia, fatigue, headache, nausea or vomiting, or diarrhoea or (2) at least one respiratory sign or symptom (including cough, shortness of breath), new olfactory or taste disorder, or radiographic evidence of COVID-19–like pneumonia. Upon the report of any suspicious COVID-19 symptoms, a nasopharyngeal specimen would be obtained at the clinical trial site, and RT-PCR would be performed at a central laboratory. In cases of negative RT-PCR tests, participants underwent further RT-PCR tests after 48 hours unless their symptoms regressed. Positive RT-PCR tests would indicate definitive symptomatic COVID-19.

**Reviewer**

3. Page 10 line 5: Need to define "seroconversion rate", e.g. how many fold-increase, in the text. Currently it is only defined in a table footnote.

**Authors**

Thank you for your comment. Amended. The Exploratory Immunogenicity Endpoints sub-heading in the methods section was revised, and the following sentence was included:

Seroconversion was defined as a post-vaccination IgG titer that was at least four-fold higher than the baseline titer.

**Reviewer**

4. Page 10 line 21: More descriptive information is needed for the sampling for investigation of variants, e.g. from all cities?

**Authors**

Thank you for your meticulous comment. Given the occurrence of SARS-CoV-2 Delta variant amid this phase III trial [3], variant detection was conducted in the study. Due to recources constraints in other trial sites, this procedure was only available in Tehran, the main trial site with 43.6% of participants. Using the convenience sampling method, 151 samples were obtained from 913 participants at Tehran trial site who became symptomatic for COVID-19, and underwent variant detection. The authors also acknowledged this limitation in the Strenghths and Limitations section of the manuscript, which now reads:

Given the occurrence of the SARS-CoV-2 Delta variant amid this phase III trial [3], variant detection was conducted in the study. Due to resource constraints in other trial sites, this procedure was only available in Tehran, the main trial site with 43.6% of participants. Using the convenience sampling method, 151 samples were obtained from 913 participants at Tehran trial site who became symptomatic of COVID-19 and underwent variant detection.

**Reviewer**

5. Page 10 line 31: Efficacy was evaluated among participants who were "fully vaccinated and did not deviate from the study protocol". In what way did the excluded participants deviate from the study protocol? I can't find this information in the text or in Figure 1.

**Authors**

Thank you for your meticulous comment. We agree with the reviewer's opinion. In the placebo group, 6,495 received the second dose, among whom 39 participants were excluded (34 were lost to follow-up, 4 withdrew from the study, and one participant passed away within 14 days after the second injection). In the intervention group, 13,011 received the second dose, among whom 66 participants were excluded (55 were lost to follow-up, 10 withdrew from the study, and one participant passed away within 14 days after the second injection). In addition, Figure 1 (Figure 2 in the revised version) was revised, and more details were included to address this insightful comment.

**Reviewer 2**

Fengcai Zhu, Jiangsu Provincial Center for Diseases Control and Prevention

**Reviewer**

In this phase III clinical trial, 20,000 participants aged 18-75 years were studied, demonstrating the safety and 50.2% efficacy symptomatic COVID-19 of two doses of BIV1-CovIran vaccine (5μg vaccine with the interval of 28 days). There are a few questions that need to be resolved by the authors.

1. In Summary. The efficacy of BIV1-CovIran was primarily assessed by the onset of definitive symptomatic COVID-19 infection. Please supplement this information in the conclusion.

**Authors**

The authors would like to express their most sincere words of appreciation for your time and consideration. The comment was addressed accordingly, and the conclusion now reads:

A two-dose regimen of BIV1-CovIran vaccine conferred 50.2%, 70.5% and 83.1% efficacy against symptomatic, severe and critical COVID-19. Vaccination was well tolerated, with no safety concerns raised.

**Reviewer**

2. In introduction. "We previously reported Phase I and Phase II safety and immunogenicity results from clinical trials of BIV1-CovIran vaccine" The results are under review, so "reported" can be changed to "evaluated". Authors should mark these results as "not published yet".

**Authors**

Thank you for your comment. The paper reporting the results of the phase I and phase II clinical trials is now published in BMJ Open [4]. We double-checked the manuscript and inserted the citation wherever appropriate.

**Reviewer**

3. In Methods. How was blinding done? The method used to generate the random allocation sequence, type of randomisation and details of any restriction (such as blocking and block size) were not provided. Please supplement mechanism used to implement the random allocation sequence (such as sequentially numbered containers) and describing any steps taken to conceal the sequence until interventions were assigned.

**Authors**

Thank you for your comment. The section was revised, and further details were included. The paragraphs now read:

Sample Size

The sample size was calculated based on the WHO recommendation of achieving 150 cases across the vaccine/placebo groups, with an ultimate efficacy of 60% (lower bound of 30%). Estimating the COVID-19 incidence rate of 1% among the unimmunised population in Iran and 10% dropout rate, a total of 20,000 participants was required. The number of participants in each city was cardinally determined commensurate with the city population, where each trial site was located. To match the study population's age distribution to the age pyramid of the country [1], 20% of the study population in each city included participants aged 51-75 years. Within each city, participants were randomly assigned to the intervention/placebo groups with a ratio of 2:1, respectively.

Randomisation and Enrollment

Using an electronic tool [2], the randomisation sheet subsuming block sequences of 3 and 6 was produced. Upon enrollment of each eligible participant using the electronic tool [2], a unique four-character randomisation code was generated. Then, four other letters were added to the randomisation code: the first two letters of the participant's first name and the first two letters of their last name to form the participant's unique code. During the trial, all procedures were performed using the participant's unique code, and the identification information remained confidential by the principal investigator.

Concealment and Blinding

Vaccine and placebo vials were manufactured with the same appearance, label, and participant unique code, to ensure the blindness of participants, researchers, and outcome assessors. After the vaccine or placebo administration, the participant's unique code and administration date were written on the outer packaging box, and the label was recorded on the randomisation sheet. The study personnel checked all the information before vaccine/placebo administration. During the study, all packages

were archived and maintained. In cases of any emergency events, including serious AEs, the query of emergency decoding and unblinding would urgently be requested by the principal investigator.

**Reviewer**

4. Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions?

**Authors**

Thank you for your comment. The section was revised, and further details were included. The paragraphs now read:

Randomisation and Enrollment

Using an electronic tool [2], the randomisation sheet subsuming block sequences of 3 and 6 was produced. Upon enrollment of each eligible participant using the electronic tool [2], a unique four-character randomisation code was generated. Then, four other letters were added to the randomisation code: the first two letters of the participant's first name and the first two letters of their last name to form the participant's unique code. During the trial, all procedures were performed using the participant's unique code, and the identification information remained confidential by the principal investigator.

**Reviewer**

5. Please provide the formula for calculating vaccine efficacy, if possible.

**Authors**

Thank you for your comment. The statistical analysis section was revised, and further details were included. The section now reads:

Vaccine efficacy was calculated using a Poisson regression compared to the placebo group, defining the dependent variable as the number of incident cases, the independent variable as the treatment group, and the offset as the person-years. Efficacy analysis was performed on the efficacy population, who were fully vaccinated and had a vaccine/placebo administration interval of 28 ±3 days. Efficacy was assessed by the onset of COVID-19 among the efficacy population who were followed for 90 days after the second dose. The maximum contribution of each participant to person-time equalled 0.246 (90/365) person-years. Simultaneously, the vaccine efficacy against severe and critical cases of COVID-19 and deaths due to COVID-19 was analysed. Considering the study population size during this phase III clinical trial, it was assumed that missing covariates at baseline would not significantly affect the vaccine efficacy calculation and were not imputed.

$$Vaccine\ efficacy\ (\%) = \left(1 - \frac{\text{Incidence density of intervention group}}{Incidence\ density\ of\ placebo\ group}\right) \times 100$$

$$Incidence\ density = \left(\frac{\#\ confirmed\ cases\ during\ the\ effective\ follow-up}{\#observation\ years\ of\ all\ vaccinated\ participants}\right) \times 100$$

In addition, an exploratory post hoc analysis was performed to assess the subclass group vaccine efficacy analysis based on study sites, sex, age groups, and baseline serology (IgG or IgM) status. Interaction testing between subgroups was not performed due to limited statistical power.

Safety analysis was performed among the safety population, defined as participants who received at least one injection dose throughout the study. The exploratory humoral immunogenicity assessment was conducted for a subgroup of participants who had randomly received the vaccine/placebo with blood collection before and after each injection. Frequency (per cent), mean, and standard deviation (SD) were used to elucidate the data. Chi-Square ($\chi 2$) and Fisher's Exact tests were applied to evaluate categorised variables. The groups were compared with a two-sample t-test at a two-sided 5% significance level. The statistical analyses were carried out using R statistical packages v3.4.3 (http://www.r-project.org, RRID: SCR_001905). Data visualisations were performed using Tableau Desktop, version 2020.1, an interactive data visualisation software.

**Reviewer**

6. In Results. Dates defining the periods of recruitment and follow-up were not provided.

**Authors**
Thank you for your encouraging comment. We included a figure, Figure 1, which presents the mapping of the timeline of phase III clinical trial with the time trend of COVID-19 weekly new cases and mortality in Iran.
**Reviewer**
7. In Figure 1, please add the specific meaning of "Other reasons" in the figure legend.
**Authors**
Thank you for your comment. Figure 1 (Figure 2 in the revised version) was revised and more details were provided.
**Reviewer**
8. In Discussion, Paragraph 4. In our preliminary analysis, we found efficacy of 83% against the dominant variant. It seems inappropriate to use efficacy data against critical COVID-19 here, 50.2% may be more appropriate.
**Authors**
Thank you for your meticulous comment. We double-checked and revised the paragraph, which now reads:
In our preliminary analysis, we found a vaccine efficacy of 50% against symptomatic COVID-19, and 83% against critical COVID-19 at the time of the study.
**Reviewer**
9. P3 line 44 (In Summary): "among vaccinated participants, a total of 758 (5.7%), 141 (1.1%) and seven (0.1%) symptomatic, severe, and critical COVID-19 cases were reported during the 90-day follow-up after the second injection". There is one data error, 141 (1.1%) should be replaced with 144 (1.1%).
**Authors**
Thank you for your meticulous comment. Amended.
**Reviewer**
10. P6 lines 24-28/33-37: Unpublished literature is cited in many places as reference.
**Authors**
We apologise for the inconvenience. Kindly be informed that the paper reporting the results of the phase I and phase II clinical trials is now published in BMJ Open [4]. We double-checked the manuscript and inserted the citation wherever appropriate. The protocol was also included as a supplement for your kind consideration.
**Reviewer**
11. What is the strain used to produce inactivated vaccines?
**Authors**
Thank you for your meticulous comment. Amended. The revised sentence in the methods section now reads:
The SARS-CoV-2 virus used in vaccine production was isolated from the nasopharyngeal specimen of an Iranian patient with COVID-19, and had 99.9% identity to the earliest detected strain, Wuhan Hu-1 [6].
**Reviewer**
12. Page13 line1 Trouble! There is a problem with the expression of the sentence.
**Authors**
Thank you for your meticulous comment. The sentence was revised and now reads:
Most ARs were mild or moderate in severity (Grade 1 or 2) and were transient and self-limiting, without the need for special consideration (Table 5 and Table S2).
**Reviewer**
13. Page13 line29 Incomplete sentences.
**Authors**
Thank you for your meticulous comment. The sentence was revised and now reads:
The exploratory immunogenicity analysis results among seronegative participants are presented in Table S5.

**References**


1 Statistical Center of Iran > Iran Statistical Yearbook > Iran Statistical Yearbook 2019-2020. https://www.amar.org.ir/english/Iran-Statistical-Yearbook/Iran-Statistical-Yearbook-2019-2020 (accessed 4 Jun 2022).

2 Sealed Envelope | Randomisation (randomization) and online databases for clinical trials. https://www.sealedenvelope.com/ (accessed 4 Jun 2022).

3 Weekly epidemiological update on COVID-19 - 8 June 2021. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---8-june-2021 (accessed 17 Oct 2021).

4 Mohraz M, Salehi M, Tabarsi P, *et al.* Safety and immunogenicity of an inactivated virus particle vaccine for SARS-CoV-2, BIV1-CovIran: findings from double-blind, randomised, placebo-controlled, phase I and II clinical trials among healthy adults. *BMJ Open* 2022;**12**:e056872. doi:10.1136/BMJOPEN-2021-056872

5 Individuals using the Internet (% of population) - Iran, Islamic Rep. | Data. https://data.worldbank.org/indicator/IT.NET.USER.ZS?locations=IR (accessed 4 Jun 2022).

6 Abdoli A, Aalizadeh R, Aminianfar H, *et al.* Safety and potency of BIV1-CovIran inactivated vaccine candidate for SARS-CoV-2: A preclinical study. *Rev Med Virol* 2021;:e2305. doi:10.1002/RMV.2305

7 Ella R, Reddy S, Blackwelder W, *et al.* Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. *Lancet* 2021;**0**. doi:10.1016/S0140-6736(21)02000-6

8 Organization WH. Evidence assessment: Sinopharm/BBIBP COVID-19 vaccine. 2021-04-29)[2021-08-21]. https//cdn. who. int/media/docs/default-source/immunization/sage/2021/april/2_sage29apr2021_critical-evidence_sinopharm. pdf. 2021.

9 Falsey AR, Sobieszczyk ME, Hirsch I, *et al.* Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. *N Engl J Med* 2021;**385**:2348–60. doi:10.1056/NEJMOA2105290/SUPPL_FILE/NEJMOA2105290_DATA-SHARING.PDF

10 Voysey M, Clemens SAC, Madhi SA, *et al.* Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet (London, England)* 2021;**397**:99–111. doi:10.1016/S0140-6736(20)32661-1

11 Thomas SJ, Moreira ED, Kitchin N, *et al.* Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. *N Engl J Med* 2021;**385**:1761–73. doi:10.1056/NEJMOA2110345/SUPPL_FILE/NEJMOA2110345_DATA-SHARING.PDF

12 Tanriover MD, Doğanay HL, Akova M, *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. *Lancet* 2021;**398**:213–22. doi:10.1016/S0140-6736(21)01429-X/ATTACHMENT/FE68B092-E0A8-4AB0-A284-89D484409B3A/MMC1.PDF

13 Organization WH. Therapeutics and COVID-19: living guideline, 24 September 2021. Geneva PP - Geneva: : World Health Organization https://apps.who.int/iris/handle/10665/345356

14 Kaabi N Al, Zhang Y, Xia S, *et al.* Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. *JAMA* 2021;**326**:35–45. doi:10.1001/JAMA.2021.8565

15 Weekly epidemiological update on COVID-19 - 4 May 2021. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---4-may-2021 (accessed 6 Jun 2022).

16 Liu Y, Rocklöv J. The reproductive number of the Delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus. *J Travel Med* 2021;**28**. doi:10.1093/JTM/TAAB124

17 Elizabeth Halloran M, Struchiner CJ, Longini IM. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. *Am J Epidemiol* 1997;**146**:789–803.

doi:10.1093/OXFORDJOURNALS.AJE.A009196
18 Pajon R, Doria-Rose NA, Shen X, *et al.* SARS-CoV-2 Omicron Variant Neutralization after mRNA-1273 Booster Vaccination. *N Engl J Med* 2022;**386**:1088–91. doi:10.1056/NEJMC2119912
19 McCallum M, Czudnochowski N, Rosen LE, *et al.* Structural basis of SARS-CoV-2 Omicron immune evasion and receptor engagement. *Science (80- )* 2022;**375**:894–8. doi:10.1126/SCIENCE.ABN8652/SUPPL_FILE/SCIENCE.ABN8652_SM.PDF
20 Burki TK. Omicron variant and booster COVID-19 vaccines. *Lancet Respir Med* 2022;**10**:e17. doi:10.1016/S2213-2600(21)00559-2
21 Chenchula S, Karunakaran P, Sharma S, *et al.* Current evidence on efficacy of COVID-19 booster dose vaccination against the Omicron variant: A systematic review. *J Med Virol* 2022;**94**. doi:10.1002/JMV.27697
22 Dolgin E. Omicron is supercharging the COVID vaccine booster debate. *Nature* Published Online First: 2 December 2021. doi:10.1038/D41586-021-03592-2
23 Hoffmann M, Krüger N, Schulz S, *et al.* The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic. *Cell* 2022;**185**:447-456.e11. doi:10.1016/J.CELL.2021.12.032
24 Au WY, Cheung PP-H. Effectiveness of heterologous and homologous covid-19 vaccine regimens: living systematic review with network meta-analysis. *BMJ* 2022;**377**:e069989. doi:10.1136/BMJ-2022-069989
25 Li X. Omicron: Call for updated vaccines. *J Med Virol* 2022;**94**:1261–3. doi:10.1002/JMV.27530