PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Relative vaccine effectiveness against Delta and Omicron COVID-19 after homologous inactivated vaccine boosting: a retrospective cohort study
AUTHORS	Tang, Lin; Zhang, Yanyang; Wang, Fuzhen; Wu, Dan; Qian, Zhao-Hui; Zhang, Rui; Wang, Ai-Bin; Huang, Chang; Wang, Haifeng; Ye, Ying; Lu, Mingxia; Wang, Changshuang; Ma, Ya-ting; Pan, Jingjing; Li, Ya-fei; Lv, Xiao-Ya; An, Zhijie; Rodewald, Lance; Wang, Xuan-Yi; Shao, Yi-Ming; Wu, Zhi-Yin; Yin, Zundong

VERSION 1 – REVIEW

REVIEWER	Noor, Rashed Independent University
REVIEW RETURNED	24-Apr-2022

GENERAL COMMENTS	Manuscript Title: Relative vaccine effectiveness against Delta and Omicron COVID-19 after homologous inactivated vaccine boosting: a retrospective cohort study Manuscript ID: bmjopen-2022-063919 The retrospective cohort study using a time-dependent Cox regression model conducted by Lin Tang, Yan-Yang Zhang and colleagues showed the relative vaccine effectiveness of COVID-19 vaccines (including the homologous booster doses) against 379 Delta variant infected individuals and 405 Omicron variant infected individuals. This study demonstrated the booster dose aided protection from symptomatic infection caused by the Omicron variant. The manuscript has been logically written although at some points the authors need to fix the language issue and illustrate the explanation specifically. Methods are sound but need some elaborative description at points; however, results are clear to understand; and the result interpretations have been done in an appropriate way. Although the findings of this study apparently don't bring that much new information (since already we know that booster vaccination works very well to restore the memory B cells); yet the work demands credit because of its study designing mode; and the results reconfirming the effectiveness of booster doses along with demographic variations. Indeed, lots of papers have been published on SARS-CoV-2 variants and COVID-19 vaccines even at the end of COVID-19 pandemic; nevertheless, the knowledge from this very work may also be considered to propagate to the general readers and scientific community. Before that, authors need to address the following specific comments: Page 4, Lines 37-40: In the conclusion of the abstract, authors simply wrote: "Protection from Delta and Omicron COVID-19 declined over time, notably 6 months after primary vaccination. A

	homologous inactivated booster dose restored protection against both variants." I don't find any new information from such statement. This is already known although this is new in relation to the samples used in this study. Yet, the authors should re-think on it, and can revise this portion using some immunological terms. They should emphasize on the instigation of memory B cells later in the text. Another factor is about the timing. Indeed, 6 months after the primary dose is too long and it's expected that the neutralizing antibodies will diminish. Usually, within 2 months the secondary dose is given; and the booster dose is administered within 6 months. Authors must clarify such discrepancy in their study elsewhere. Authors tried to include these points in page 5; however, it's not clearly written what new point this particular study is adding. Page 6, Lines 14-15: Authors should add the exact date of vaccination statistics given. Lines 26-27: The rationale of the current study is missing. It's better to explain the objective of the current study in few lines here. Line 36: It's better to put the exact number of population in a scientific paper instead of "100 million". Line 40: "in all of China" or "All over China" Lines 42-43: Please mention the vaccine names with their manufacturers. Lines 48-49: Grammatical issue. Line 55: Please avoid the active sentences. Along the entire the manuscript, passive mode of write up is suggested. Page 7, Line 5: Why the word "AND" is in caps? Better write "and". Line 14: Authors may elaborate the symptoms including ARDS (if any) so that it would be easier to understand for the general readers. Lines 21-22: "For confirmed" should be "For the confirmed……" Lines 22-24: This line should be rephrased with appropriate grammar. Line 28: What do the authors mean by "infection status"? Please elaborate. Actually, it would be very much useful if the authors could provide any Table for explaining lines 28-38; otherwise it seems a bit superficial. Line 46: Can the authors explain the term "hazard ratio"? Page 8, Lines 6-14: Regarding "Patient and Public Involvement statement", the editorial policy must be followed exactly. I am not sure the why the patients' consents were not taken. If the authors clarify this point appropriately, I am happy to agree with that if the journal's policy is met. Authors may add a footnote regarding this below Table 1. Lines 40-41, 49: Can the authors clarify more about "breakthrough infections"? Page 12, Line 22: What does "-3% of Delta outbreak" mean? Line 42: At several places authors "real world". What is meant by "real world"? How about timing? How about the geographical locations? This term brings about complications. Authors may think to replace this term by a suitable word or drop it. Page 13, Line 27: "Age was risk factor for pneumonia in our study." This is so common. Hundreds of research groups found it. What's the new thing behind this statement? Is there any involvement of pre-disposing factors according to age? Page 14: Please elaborate the conclusion with some immunological terms in benefit of booster dose of vaccines. Cite

	some of the recent publications regarding booster dose in the Discussion section.

REVIEWER	Munawwar, Arshi Institute of Human Virology, Division of Vaccine Research
REVIEW RETURNED	13-Jul-2022

GENERAL COMMENTS	The whole paper is very unclear and not interesting to the specialized audience. Standard of English is not acceptable for publication, full of typographical errors and completely fails to attract readers.

REVIEWER	Tafuri, Silvio Universita degli Studi di Bari Aldo Moro, Department of Biomedical Science and Human Oncology
REVIEW RETURNED	31-Aug-2022

GENERAL COMMENTS	thank you for choosing me as a reviewer for the article titled "Relative vaccine effectiveness against Delta and Omicron COVID-19 after homologous inactivated vaccine boosting: a retrospective cohort study". I read it attentively and have the following comments: 1. The article is very interesting in terms of both topic and design. Though starting from a very simple concept, the authors were clever to exploit the momentum of the mentioned COVID-19 outbreaks and thus described effectively the relative VE against the two VOCs which are currently dominant worldwide. Therefore, the study does contribute to medical research not only in the Chinese context, but worldwide as well. I did not find any meaningful fault in the article; however, there is a few grammatical missteps which would benefit from a general text revision (e.g., line 49 "subjects under 20 years old [20 years of age]"). This is just a suggestion, though, as the overall quality of English is adequate.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Rashed Noor, Independent University

Comments to the Author:

Manuscript Title: Relative vaccine effectiveness against Delta and Omicron COVID-19 after homologous inactivated vaccine boosting: a retrospective cohort study

Manuscript ID: bmjopen-2022-063919

The retrospective cohort study using a time-dependent Cox regression model conducted by Lin Tang, Yan-Yang Zhang and colleagues showed the relative vaccine effectiveness of COVID-19 vaccines (including the homologous booster doses) against 379 Delta variant infected individuals and 405 Omicron variant infected individuals. This study demonstrated the booster dose aided protection from symptomatic infection caused by the Omicron variant. The manuscript has been logically written although at some points the authors need to fix the language issue and illustrate the explanation specifically. Methods are sound but need some elaborative description at points; however, results are clear to understand; and the result interpretations have been done in an appropriate way. Although the

findings of this study apparently don't bring that much new information (since already we know that booster vaccination works very well to restore the memory B cells); yet the work demands credit because of its study designing mode; and the results reconfirming the effectiveness of booster doses along with demographic variations.

Indeed, lots of papers have been published on SARS-CoV-2 variants and COVID-19 vaccines even at the end of COVID-19 pandemic; nevertheless, the knowledge from this very work may also be considered to propagate to the general readers and scientific community. Before that, authors need to address the following specific comments:

Response: We appreciate the positive feedback on the study and manuscript. When this study was conducted, there were very few Omicron infections in the mainland of China, and this study provided one of the earliest evaluations of relative VE and population immunity in China. The study has proven to be useful for refining methods to assess population immunity (as indicated by this reviewer's comment above), and is being used nationally in appropriate settings.

Page 4, Lines 37-40: In the conclusion of the abstract, authors simply wrote: "Protection from Delta and Omicron COVID-19 declined over time, notably 6 months after primary vaccination. A homologous inactivated booster dose restored protection against both variants." I don't find any new information from such statement. This is already known although this is new in relation to the samples used in this study. Yet, the authors should re-think on it, and can revise this portion using some immunological terms. They should emphasize on the instigation of memory B cells later in the text.

Response: We agree with the reviewer that it is known that protection declines over time for COVID-19 vaccines and that booster doses restore protection. But as the reviewer also points out, this is newly known with the mix of vaccines used in China (our samples), and because the evaluation is based on observations of protection rather than from immunogenicity studies (where the decline in antibody levels has been well documented), the new data from this study was and remains important for giving confidence to public health officials and the public that the vaccines are working and that they need boosting to sustain protection. Our study was the first to evaluate relative vaccine effectiveness against Delta and Omicron variants at the same period and the same province in China's infection-naïve population. By evaluating population-level protection from COVID-19 pneumonia that was built by a provincial immunization program with China-produced vaccines that were used as recommended by China's National Health Commission, the study addressed policy-level questions.

We also agree that the likely mechanism is activation of memory B cells. However, since we did not study immune markers, we do not feel that we can make a conclusion about memory B cells. To address this comment, we did two things. We restated our conclusion in the Abstract about protection to make it clear that the results address the question raised (relative effectiveness, decline by six months, and restoration of protection with booster doses), and we added information in the Discussion about the likely mechanism being activation of memory B cells (with references to immunogenicity studies of antibody waning and rapid increase with boosting).

The new text in the Abstract and in the Conclusion of the Discussion section is, "COVID-19 vaccination in China provided good protection against symptomatic COVID-19 and COVID-19 pneumonia caused by Delta and Omicron variants. Protection declined 6 months after primary series vaccination but was restored by homologous inactivated booster doses given 6 months after the primary series."

The new text in the Discussion is about memory B cells is, "In China, inactivated vaccines were implemented widely, and a similar decline of neutralizing titers was also observed. Immunogenicity of homologous booster

doses of inactivated vaccine has been illustrated in clinical trials[7 27], and the likely mechanism for booster dose immunogenicity and corresponding effectiveness is activation of memory B cells induced by primary series vaccination."

Another factor is about the timing. Indeed, 6 months after the primary dose is too long and it's expected that the neutralizing antibodies will diminish. Usually, within 2 months the secondary dose is given; and the booster dose is administered within 6 months. Authors must clarify such discrepancy in their study elsewhere. Authors tried to include these points in page 5; however, it's not clearly written what new point this particular study is adding.

Response: The reviewer makes an important point. The timing of the booster dose is very important. If given too early, the memory B cells may not have had time to mature. If given too late, there may be loss of protective efficacy. Because neutralizing antibody titers do not correlate perfectly with protection (at least with the inactivated vaccines), the timing of loss of protection that we found in this study proved to be important for technical policy making.

We agree with the reviewer's concern that a second dose is given at 2 months after the first dose is too late, but the recommended timing of the second dose is 2 to 4 weeks after the first dose. The confusing wording the reviewer is referring to was in the 'what is already known', 'what this study adds' and 'how this study might affect research' sections. These sections have been deleted at the request of the Editor because they are not used in BMJ Open. We have checked the other descriptions about dose timing, and we believe that all are clearly stated.

Page 6, Lines 14-15: Authors should add the exact date of vaccination statistics given.

Response: We have made the suggested change. The new sentence is, "As the end of July 2022, over 3.4 billion doses of these vaccines have been used in China, and more than 2 billion doses have been procured for overseas use."

Lines 26-27: The rationale of the current study is missing. It's better to explain the objective of the current study in few lines here.

Response: We have done so. We now explain the rationale of the study by stating, "The outbreaks provided an opportunity to evaluate variant-specific breakthrough infection rates and relative protective effectiveness of homologous inactivated COVID-19 vaccine booster doses against symptomatic infection and pneumonia."

Line 36: It's better to put the exact number of population in a scientific paper instead of "100 million".

Response: We agree and have made the suggested change. The sentence now says, "The setting was Henan province where there were two simultaneous outbreaks. Henan has a population of 99.36 million people."

Line 40: "in all of China" or "All over China"

Response: We rewrote the sentence so that it now says, "The COVID-19 prevention and control policy in the mainland of China requires that all SARS-CoV-2 infections are traced, and contacts quarantined for at least two weeks and tested periodically in quarantine."

Lines 42-43: Please mention the vaccine names with their manufacturers.

Response: We now include all of the brand names. The updated description of the vaccines states, “The COVID-19 vaccines used in the outbreak setting were two inactivated COVID-19 vaccines - BBIBP-CorV (Sinopharm, Beijing CNBG) and CoronaVac (Sinovac,Co., Ltd), accounting for 91.8% of vaccines used; a protein subunit vaccine, Zifivax (Zhifei Longcom, 7.5%); and an adenovirus5-vectored vaccine, Convidecia (Cansino, 0.7%).”

Lines 48-49: Grammatical issue.

Response: We rewrote the sentence, which now says, “On January 8, a medical device company employee and a middle school student both tested positive for SARS-CoV-2 infection when seeking health care in Anyang. Investigation revealed an Omicron outbreak in a boarding school with 4,103 students and teachers along with community transmission.”

Line 55: Please avoid the active sentences. Along the entire the manuscript, passive mode of write up is suggested.

Response: As the reviewer noted, we tend to use the active voice throughout. This is because the authors were responsible for conducting the study. We reviewed the voice of the five most read articles listed on the *BMJ Open* website on September 10, 2022. Four of the five used active voice or mixed active and passive voice, and one used passive voice exclusively. Our preference therefore is to continue to use the active voice since it appears consistent with journal style and reflects that the authors actively did the study.

Page 7, Line 5: Why the word “AND” is in caps? Better write “and”.

Response: We originally put “and” in upper case to show that it is a Boolean variable. We have changed it to lower case as the reviewer suggests.

Line 14: Authors may elaborate the symptoms including ARDS (if any) so that it would be easier to understand for the general readers.

Response: The reviewer makes an important point since the symptoms are part of the official case definitions. Although adult respiratory disease syndrome is not included in the case definition, we reviewed and modified this section to show that some elements of the definition were subjective symptoms, and other elements of the definition were objective actions. The new wording is “Thus, the outcome definitions included subjective symptoms (e.g., sore throat and headache), elicited signs (e.g., fever, altered mental status, pneumonia on imaging), and objective health care actions (e.g., ICU admission and mechanical ventilation), with the more objective elements for the more severe outcomes.”

Lines 21-22: “For confirmed” should be “For the confirmed……”

Response: We made the suggested change.

Lines 22-24: This line should be rephrased with appropriate grammar.

Response: We have modified the sentence so that it now says, “For the confirmed SARS-CoV-2 infections, we reviewed medical records from designated COVID-19 management hospitals in Zhengzhou and Anyang to abstract clinical management data, laboratory testing and results, and chest imaging and results.”

Line 28: What do the authors mean by "infection status"? Please elaborate. Actually, it would be very much useful if the authors could provide any Table for explaining lines 28-38; otherwise it seems a bit superficial.

Response: We have modified the sentence to make it clear that the investigators were blind to outcome when determining vaccination status. The new sentence is, "Without knowledge of whether subjects had SARS-CoV-2 infection or not, we obtained vaccination records from the national vaccination database using subjects' national IDs." We think that the clarified sentence will be sufficient and that a new table is not needed.

Line 46: Can the authors explain the term "hazard ratio"?

Response: This is an important part of the methods. We added a definition of the hazard ratio to the sentence, which now reads, "The reference group was primary vaccination ≥180 days before exposure; rVE was 1-adjusted hazard ratio (ratio of incidences of the outcome of interest between the two vaccination groups) for COVID-19 symptomatic infection or pneumonia."

Page 8, Lines 6-14: Regarding "Patient and Public Involvement statement", the editorial policy must be followed exactly. I am not sure the why the patients' consents were not taken. If the authors clarify this point appropriately, I am happy to agree with that if the journal's policy is met. Authors may add a footnote regarding this below Table 1.

Response: We conducted the study using data required to be obtained on all contacts of cases and on all infected individuals. It is a public health duty to evaluate the effectiveness of the vaccines recommended. Since the data were all required elements of routine data collection, it is not feasible or necessary to obtain consent. We believe that the "Patient and Public Involvement statement" is completely accurate and meets the journal's standards.

Lines 40-41, 49: Can the authors clarify more about "breakthrough infections"?

Response: This is an important definition. A breakthrough infection is an infection that occurs after vaccination against the disease – usually at least 2 weeks after the vaccination series so that the immune system has a chance to respond. We define breakthrough infection in the Methods section in the Data analysis subsection, stating, "A breakthrough infection was an RT-PCR-confirmed SARS-CoV-2 infection at least 14 days after completion of primary vaccination."

Page 12, Line 22: What does "-3% of Delta outbreak" mean?

Response: We appreciate the reviewer pointing out that that the dash can also be interpreted as a mathematical symbol. We removed the dash and clarified the sentence to now say, "Our study also found a higher breakthrough infection rate in the Omicron transmission chain than the Delta chain (22% vs 10%) and found no severe Omicron cases and only 12 severe Delta cases, representing 3% of the Delta outbreak cases."

Line 42: At several places authors "real world". What is meant by "real world"? How about timing? How about the geographical locations? This term brings about complications. Authors may think to replace this term by a suitable word or drop it.

Response: "Real world study" is a term that has come to more prominence in the COVID-19 pandemic. It simply refers to an observational study, as opposed to an experimental study in which individuals are assigned treatments.

Page 13, Line 27: "Age was risk factor for pneumonia in our study." This is so common. Hundreds of research groups found it. What's the new thing behind this statement? Is there any involvement of pre-disposing factors according to age?

Response: Although this is known from other studies, it is a result from this study, and we simply report it as a result. We do not claim that it is a new finding. To address the reviewer's point, we added the phrase "Consistent with what is well known about COVID-19" to the sentence, which now says, "Consistent with what is well known about COVID-19, older age was risk factor for pneumonia in our study."

Page 14: Please elaborate the conclusion with some immunological terms in benefit of booster dose of vaccines. Cite some of the recent publications regarding booster dose in the Discussion section.

Response: To address this comment and the reviewer's first comment, we now mention that the effect of the booster dose is likely because of activation of memory B cells. The new sentence in the Discussion is "Immunogenicity of homologous booster doses of inactivated vaccine has been illustrated in clinical trials [7 27], and the likely mechanism for booster dose immunogenicity and corresponding effectiveness is activation of memory B cells induced by primary series vaccination."

Reviewer: 2

Dr. Arshi Munawwar, Institute of Human Virology

Comments to the Author:

The whole paper is very unclear and not interesting to the specialized audience. Standard of English is not acceptable for publication, full of typographical errors and completely fails to attract readers.

Response: We have to disagree with the reviewer's point that this is not interesting, as this particular study has been important to add confidence the protective immunity being developed by the inactivated vaccines produced in China. The study has been of considerable interest to policy makers and therefore to public health professionals and scientists. Additionally, since this is pure vaccine-induced immunity (there is almost no hybrid immunity in China), this study provides a window on pure vaccine-induced protection.

Regarding the interest level, the first reviewer said, "the knowledge from this very work may also be considered to propagate to the general readers and scientific community" and that "the work demands credit because of its study designing mode; and the results reconfirming the effectiveness of booster doses along with demographic variations." The third reviewer said the study is "very interesting in terms of both topic and design," further stating that "the study does contribute to medical research not only in the Chinese context, but worldwide as well."

Regarding the standard of English, the first reviewer stated that the manuscript "logically written" and the third reviewer said that English is "adequate." Both reviewers provided some specific suggestions to clarify the writing, and we have adjusted the manuscript in accordance with their grammar suggestions.

Reviewer: 3

Prof. Silvio Tafuri, Universita degli Studi di Bari Aldo Moro

Comments to the Author:

Dear Editor,

thank you for choosing me as a reviewer for the article titled "Relative vaccine effectiveness against Delta and Omicron COVID-19 after homologous inactivated vaccine boosting: a retrospective cohort study". I read it attentively and have the following comments:

1. The article is very interesting in terms of both topic and design. Though starting from a very simple concept, the authors were clever to exploit the momentum of the mentioned COVID-19 outbreaks and thus described effectively the relative VE against the two VOCs which are currently dominant worldwide. Therefore, the study does contribute to medical research not only in the Chinese context, but worldwide as well. I did not find any meaningful fault in the article; however, there is a few grammatical missteps which would benefit from a general text revision (e.g., line 49 "subjects under 20 years old [20 years of age]"). This is just a suggestion, though, as the overall quality of English is adequate.

Response: We appreciate the reviewer's attentive review and positive comments on our manuscript. With regard to the grammatical missteps, we have made grammatical changes suggested by Reviewer 1 and this reviewer (Line 49, which now states "20 years old") and we have gone through the entire manuscript carefully to find other grammatical problems.

VERSION 2 – REVIEW

REVIEWER	Noor, Rashed Independent University
REVIEW RETURNED	18-Sep-2022

GENERAL COMMENTS	Authors have addressed to my queries in appropriate way.