PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of mRNA COVID-19 Vaccines against Omicron and Delta Variants in a matched test-negative case-control study among US Veterans
AUTHORS	Young-Xu, Yinong; Zwain, Gabrielle; Izurieta, Hector S; Korves, Caroline; Powell, Ethan; Smith, Jeremy; Balajee, Abirami; Holodniy, Mark; Beenhouwer, David; Rodriguez-Barradas, Maria; Brown, Sheldon; Marconi, Vincent

VERSION 1 – REVIEW

REVIEWER	Tafuri, Silvio Universita degli Studi di Bari Aldo Moro, Department of Biomedical Science and Human Oncology
REVIEW RETURNED	20-May-2022

GENERAL COMMENTS	the paper you presented is very interesting and I recommend the pubblication in BMJ Open, pending some minor revision 1. Introduction. Please, use some sentences to introduce the topic of pandemic and of anti-SARS-COV.-2 vaccination, It is not useful starting with a reference to another study results, not described. 2. Methods. Inclusion and exclusion criteria must be presented as bullet point, for better clarity 3. Table 1 is very hard to understand. Keep attention, in some brackets there are the sign of percentanges (%), not reported in other cells. Revise for consistency and check if percentages are corrected. 4. Please, review the structure of Table 2. 5. Discussion. Please, avoid to report numbers and data yet presented in results section. 6. References. Please, discuss as comparison results from Bianchi FP, Stefanizzi P, Germinario CA, Migliore G, Vimercati L, Martinelli A, Lobifaro A, Diella G, Larocca AMV, Control Room Working Group, Tafuri S. Medium-to-Long-Term Immunogenicity of BNT162b2 mRNA COVID-19 Vaccine: A Retrospective Cohort Study. Vaccines (Basel). 2022 Mar 10;10(3):417. doi: 10.3390/vaccines10030417. PMID: 35335049; PMCID: PMC8949567.

REVIEWER	Nouatin, Odilon Centre de Recherches Médicales de Lambaréné
REVIEW RETURNED	23-May-2022

GENERAL COMMENTS	The authors present a very good manuscript, very well written with very interesting results. They also clarified the limitations of the

	study, thus answering some of my questions. However, some details can be given. • Introduction: The authors can give more details on the importance of evaluating the effectiveness of the vaccine against Omicron because obviously, this variant seems to cause fewer deaths than the others. • Results - Table 1 seems not to be too clear. Are there any missing data? the sum of the values in each category should give the number of cases or controls mentioned above? - The various comorbidities can be detailed in the table if available - Does the control group present the same comorbidities as the cases? Do those who received two doses of vaccine have the same comorbidities as those who received the booster? These informations are very interesting to reinforce the results observed. - The authors concluded that the mRNA vaccine booster is more effective against infection, hospitalization, and death than 2-dose vaccination among an older male population with comorbidities. Although the male sex represents the majority of the study population, it is not mentioned in the manuscript that the analyzes were made only in male. So what about the female? The authors may revise the conclusion. - It would also be interesting if the authors present the results separately on each type of mRNA vaccine (Pfizer-BioNTech and Moderna). - If the data collected allows it, the authors can perform a "survival test" figures to show the times to first infection, hospitalization and death in each group (control, 2 doses, booster) and on each variant (Delta and Omicron)

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: the paper you presented is very interesting and I recommend the publication in BMJ Open, pending some minor revision

Comments

1. Introduction. Please, use some sentences to introduce the topic of pandemic and of anti-SARS-COV-2 vaccination, It is not useful starting with a reference to another study results, not described.

Response: Thank you for this point. We have rewritten the introduction to better describe the topic of the global pandemic, include more studies, and point out the importance of continuing to study vaccine effectiveness against specific variants (page 6-7, line 107-147).

2. Methods. Inclusion and exclusion criteria must be presented as bullet point, for better clarity

Response: Thank you for your suggestion. We agree that this would result in better clarity. Unfortunately, it is not our style, nor do we believe it is this journal's style to have bullet points

in the main text. As a compromised, we have written the criteria as numbered points. We also included the bullet points in the appendix to help both reviewers and readers with better clarity. (Pages 8-9, lines 172-183).

3. Table 1 is very hard to understand. Keep attention, in some brackets there are the sign of percentages (%), not reported in other cells. Revise for consistency and check if percentages are corrected.

Response: Thank you for pointing out errors in our table. We have made some additions to the table for clarity and checked the numbers and percentages for accuracy. As Reviewer 2 has pointed out, there was some missing data and we have made sure to include all levels of each category to make sure the numbers add up.

4. Please, review the structure of Table 2.

Response: We have reviewed the structure of the table and added the numbers of cases and controls, more descriptive header names for the table, and added description to the notes.

5. Discussion. Please, avoid to report numbers and data yet presented in results section.

Response: We have eliminated the noted redundancies from the Discussion.

6. References. Please, discuss as comparison results from Bianchi FP, Stefanizzi P, Germinario CA, Migliore G, Vimercati L, Martinelli A, Lobifaro A, Diella G, Larocca AMV, Control Room Working Group, Tafuri S. Medium-to-Long-Term Immunogenicity of BNT162b2 mRNA COVID-19 Vaccine: A Retrospective Cohort Study. Vaccines (Basel). 2022 Mar 10;10(3):417. doi: 10.3390/vaccines10030417. PMID: 35335049; PMCID: PMC8949567.

Response: We thank the reviewer for pointing us toward an interesting study and added this reference to our revised Introduction (page 6, line 113-115).

Reviewer 2: The authors present a very good manuscript, very well written with very interesting results. They also clarified the limitations of the study, thus answering some of my questions. However, some details can be given.

Comments

1. The authors can give more details on the importance of evaluating the effectiveness of the vaccine against Omicron because obviously, this variant seems to cause fewer deaths than the others.

Response: We have rewritten the introduction to better describe the topic of the global pandemic, include more studies, and point out the importance of continuing to study vaccine effectiveness against specific variants (page 6, line 107-147).

2. Table 1 seems not to be too clear. Are there any missing data? the sum of the values in each category should give the number of cases or controls mentioned above? The various comorbidities can be detailed in the table if available.

Response: Concerns about this table were also mentioned by Reviewer 1 and we added to the table for clarity and checked the numbers and percentages for accuracy (including adding a missing level of a variable so now all categories add up). We have removed typographical errors and added comorbid conditions to the Table 1. We hope that the table is now easier to read.

3. Does the control group present the same comorbidities as the cases? Do those who received two doses of vaccine have the same comorbidities as those who received the booster? These informations are very interesting to reinforce the results observed.

Response: We have added to the Results section on this topic (page 11, line 238-241) and added comorbid conditions to Table 1.

4. The authors concluded that the mRNA vaccine booster is more effective against infection, hospitalization, and death than 2-dose vaccination among an older male population with comorbidities. Although the male sex represents the majority of the study population, it is not mentioned in the manuscript that the analyzes were made only in male. So what about the female? The authors may revise the conclusion.

Response: We have revised the conclusions, as suggested (page: 16, line 340) and (page: 4, line 84-88).

5. It would also be interesting if the authors present the results separately on each type of mRNA vaccine (Pfizer-BioNTech and Moderna).

Response: We have conducted the analyses by vaccine manufacturer (see table below). Confidence intervals overlapped, so there was no indication for a difference in adjusted VE by vaccine manufacturer. As this question was not included in the study protocol, we did not include it in the manuscript. The Table presenting the results of this post hoc analysis is below, for reference.

Variant, number of doses versus unvaccinated	Adjusted VE (95% CI)_Moderna^	Adjusted VE (95% CI)_Pfizer^
Omicron, 2nd dose	13% (10-17)	17% (14-21)
Omicron, 3rd dose	66% (64-68)	62% (60-64)
Delta, 2nd dose	57% (53-61)	47% (42-53)
Delta, 3rd dose	89% (85-92)	90% (88-93)

Above numbers exclude Johnson & Johnson's Janssen vaccines as of the date of the Johnson & Johnson's Janssen vaccine. 2nd and 3rd doses are for mRNA vaccines compared to no vaccination in the indicated variant predominant period beginning 14 days after vaccination. Tests occurring in 0-13 days after vaccination were excluded.
^Cases and controls were matched 1:4 on HHS region and date. The adjusted variables include the following: age (continuous), body mass index (missing, normal <26, overweight/obese ≥26), cancer, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, immunocompromised, priority level, race/ethnicity, and rurality.

6. If the data collected allows it, the authors can perform a "survival test" figures to show the times to first infection, hospitalization and death in each group (control, 2 doses, booster) and on each variant (Delta and Omicron)

Response: We would love to do a survival analysis, unfortunately, our data collection misses some outcomes as veterans might be diagnosed and treated for COVID-19 outside the VA system. For those who are diagnosed and treated for COVID-19 in the VA system, we are confident of capturing their vaccination history as that is one of the strengths of our study design. While the data, as collected for this study, does not allow us to perform a survival analysis, we will use survival analysis in other studies when appropriate.

VERSION 2 – REVIEW

REVIEWER	Tafuri, Silvio Universita degli Studi di Bari Aldo Moro, Department of Biomedical Science and Human Oncology
REVIEW RETURNED	29-Jun-2022

GENERAL COMMENTS	Authors rightly addressed my issues.

REVIEWER	Nouatin, Odilon Centre de Recherches Médicales de Lambaréné
REVIEW RETURNED	04-Jul-2022

GENERAL COMMENTS	The authors have brought with precision, the maximum correction to the various comments.