Dear Dr. Self,

Thank you for sending us your paper and giving us the chance to consider your work. We sent it out for external peer review and discussed it at the manuscript committee meeting.

Unfortunately we do not consider it suitable for publication in its present form. However if you are able to amend it in the light of our and/or reviewers' comments, we would be happy to consider it again.

The reviewers' comments are at the end of this letter.

The editors' comments are listed below:

We hope that you will be willing to revise your manuscript and submit it within 4-6 weeks. When submitting your revised manuscript please provide a point by point response to our comments and those of any reviewers.

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I hope you will find the comments useful. Please don't hesitate to contact me if anything is unclear or if you have any questions.

Best wishes and we look forward to your revised paper.

Yours sincerely,

Nazrul Islam, MBBS, MSc, MPH, PhD
Research Editor, The BMJ
nislam@bmj.com

**Report from The BMJ's manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair); Richard Riley (statistical advisor); Wim Weber; Navjoyt Ladher; Nazrul Islam; Di Wang; Tim Feeney
Decision: put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

** comments ***

* The VE of the third dose has been widely reported, including that on Omicron variants. Therefore, the manuscript in its current form was not evaluated as a priority by the Editorial Board. However, as we discussed, data on Omicron sub-variants may be of interest, and we look forward to the revised version with data on the sub-variants (and possibly the 4th dose) before any formal decision is made.

* With the updated data, it is also expected that additional analysis could be conducted on immunocompromised patients.

* Cases and controls were not matched, and the comparison was adjusted only for admission date (biweekly), age (with broad categories), sex, race/ethnicity, and region of the admitting hospital. Could you please comment on the adequacy of this fairly minimal adjustment. Some Editors mentioned other potentially important covariates such as comorbidities, SES, residential status, etc.

* A recent publication recommended against using Omicron hospitalization as an indicator for severe Covid-19 diseases and indicated some approaches that better characterize vaccine protection against severe Covid-19 disease caused by Omicron, e.g. indicators of respiratory distress. (https://doi.org/10.1016/j.vaccine.2022.04.069) Could you please address the issues raised by them.

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Reviewer: 1
Recommendation:

Comments:
Michael Kundi
The MS "Vaccine Effectiveness of Primary Series and Booster Doses against Omicron Variant COVID-19-Associated Hospitalization in the United States" submitted by Adams et al. is an important contribution to inform vaccination policy for reducing the risk of severe COVID-19 during the SARS-CoV-2 waves expected to affect us globally in the next months. The study does primarily provide information about the additional benefit of a booster dose after a primary vaccination course, but also indications of waning protection after both the primary doses and the booster are of great importance. The study applied a variant of the test-negative approach that is, in my view, suitable for comparison of VEs but may be biased with respect to the absolute level (point estimate) of VEs (see e.g. Dean et al. NEJM 385;15 October 7, 2021). Nevertheless, the study as previous studies by the IVY network was well designed and very thoroughly conducted. Some concerns about study methodology and reporting are addressed below.

1. Of 1,572 COVID-19 patients only in 648 (41 %) whole-genome sequencing was performed and in 78 % a variant could be identified. Among identified variants, 13 % were Delta and were excluded from further analysis. I see no point for this exclusion. Very likely the same percentage of not-Omicron variants was the infecting agent in those not submitted to WGS. But they remain in the analysis. WGS should only be used to substantiate that indeed the predominant agent in the enrolled subjects was the Omicron variant of SARS-CoV-2. I suggest to change the title to "Vaccine Effectiveness of Primary Series and Booster Doses During a Period of Omicron Variant Dominance against COVID-19-Associated Hospitalization in the United States"

2. There are some important differences between unvaccinated and vaccinated as well as between cases and controls as reported in Tables 1 and 2. Unvaccinated had less often a prior hospital visit that may point to differences in health-care seeking behavior. Another important difference is the higher rate of self-reported prior SARS-CoV-2 infection in controls. The model was not adjusted for prior infection. It seems that this information was not available for all participants (which is strange in my view and could be due to a wrong assignment of missing values for those that responded they cannot remember). I strongly recommend inclusion of prior infection at least within a sensitivity analysis that may be reported in the supplement.

3. Table 1 would benefit from columns with p-values comparing vaccinated/unvaccinated and cases/controls. Table 2 has a p-value comparing the three groups simultaneously. I’d rather like to see a comparison vaccinated/unvaccinated and primary/booster vaccinated. These comparisons are orthogonal and no adjustment is needed.

4. Although a waiver of informed consent was granted for the public health surveillance, this does not hold for the investigation of the antibody response. Nothing is specified how the patients for this study were recruited and whether or not informed consent was obtained.

5. Concerning antibody responses it should be mentioned that the BAUs are with respect to a standard pool from 2020 with antibodies against the original virus (predominantly D614G) and that values against Omicron are likely a factor of about 100 lower.

Additional Questions:
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**Institution:** Medical University Vienna, Austria

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Reviewer: 2

Recommendation:

Comments:
Thank you for the opportunity to review this easy to read manuscript on an important topic. I hope my suggestions are helpful.

1. The use of hospitalization together with a positive test is, as the authors themselves note in the Introduction, problematic in the Omicron period of dominance. It can be difficult to disentangle the “because of covid-19” hospitalizations from the “with covid-19” hospitalizations. The proportion of “with covid-19” hospitalizations becomes significant when infections are common in the population. As I understand it, the authors use signs and symptoms of covid-19 together with a PCR positive test to identify cases. But this does not ensure that the hospitalization “was because of covid-19”, i.e. you can still be admitted due to a non-covid related issue and have incidental symptomatic infection? The authors write “admitted to the hospital with COVID-19” lines 255-56. It should be clarified what this means.

2. Have the authors evaluated the admission/discharge diagnoses associated with the hospitalisations?

3. It is a weakness that no information on prior infection is included. Can previously infected individuals be excluded from the study? In table 1, self-reported prior infection is mentioned. Please provide sensitivity analyses, where patients with self-reported infection are excluded.

4. The study estimates VE with unvaccinated as a reference group. I do not think this is the most relevant comparison at this point, neither from the individual level (will I benefit from a booster) or a public health perspective (should we roll-out a booster). The most relevant comparison is booster vs primary course. I would refocus the paper with this in mind.

5. A case could be made for excluding the antibody measurements part from the manuscript. The volunteers for this part are not included in the VE part on hospitalized patients and the study periods do not align, i.e. it is essentially another mini study. The results are also not discussed in any detail, nor are they novel. The presentation of the manuscript will be improved by dropping this part.

6. Please discuss the potential weaknesses of the test-negative design in this scenario in more detail – see e.g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6888869/#BX2.

7. Generalizability; these are older hospitalized patients (maybe add “older adults” to the title). Can these results be used to support 18+ recommendations in the general non-hospitalized population?

Anders Hviid, Msc, DrMedSci,
Department of Epidemiology Research, Statens Serum Institut,
Copenhagen, Denmark

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In this multicenter observational case-control study using the test-negative design from 21 hospitals in the US, Adams and colleagues aimed to estimate the vaccine effectiveness of primary series and booster doses against Omicron variant Covid-19-associated hospitalizations. A total of 3,181 adults who were hospitalized with an acute respiratory illness were included. Participants included 1,572 (49%) "case-patients" with laboratory confirmed COVID-19 and 1,609 (51%) control patients who tested negative for SARS-CoV-2. The authors find that vaccine effectiveness against Omicron COVID-19 hospitalization for a primary series plus one booster of any vaccine product dose was 77% (95% CI: 71–82%), and for a primary series alone was 44% (95% CI: 31–54%) (p<0.001). They further found that vaccine effectiveness was higher for a boosted regimen than a primary series alone. The authors concluded that among immunocompetent people, a booster dose of COVID-19 vaccine provided additional benefits beyond a primary vaccine series alone for preventing COVID-19 hospitalization due to the Omicron variant.

While the topic of the study is of interest for a general readership, I am concerned by two methodological aspects that I believe limit the interpretability of the findings and generalizability to the target population.

1. The authors used the so-called test-negative design in which cases status is defined by a positive test, here against SARS-CoV-2. The test-negative group has similar symptoms (i.e., respiratory infections) cause by another virus, e.g., influenza. The underlying conception for this design assumes that if two (or more) viruses do not interact and circulate independently, then the frequency of co-detection estimated from cross-sectional data should be approximately equal to the product of each virus's detection frequency. Conversely, any significant deviation from equality should then indicate interaction. While this study design has been uses in other studies, the fundamental validity of this design has hardly been tested. In a recent paper by Domenech de Celis and colleagues (https://doi.org/10.1098/rspb.2021.2358), the fundamental principles of the test-negative design have been challenged. The authors of that paper show that by focusing on the pair influenza –SARS-CoV-2, the prevalence ratio systematically underestimates the strength of interaction, and can even misclassify antagonistic or synergistic interactions that persist after clearance of infection. Overall, this paper suggests that ecological or epidemiological studies based on co-detection prevalence data provide a poor guide to assess interactions among respiratory viruses. Consequently, inferences about vaccination effects can be equally poorly estimated from such studies.

2. As study participants all have been hospitalized, there is an inherent selection bias. As there are other reasons for hospitalizations that may not have been recorded, Selection of participants represent a collider-stratification bias. More details on the selection bias in test-negative studies can be found in a commentary by Westreich and Hudgens: https://doi.org/10.1093/aje/kww063 and in the study by Sullivan and colleagues (https://doi.org/10.1093/aje/kww064). From the analysis approach of the paper by Adams and colleagues, I do not see an attempt to correct for this bias, if that is possible at all.
Minor: I suggest that the authors do not conduct statistical null hypothesis tests to compared baseline differences of the participants.

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