Dear Dr. Prieto-Alhambra,

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, and would be happy to consider it for publication if you are willing and able to revise your paper according to the report from the manuscript meeting and the reviewers' comments.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Yours sincerely,

Di Wang
Clinical Editor, the BMJ

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**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: Wim Weber (chair), Rafael Perera (statistical editor), Sophie Cook, Timothy Feeney, John Fletcher, Nazrul Islam, Elizabeth Loder, John Powers, Joseph Ross, Emma Rourke, Tiago Villanueva, Di Wang.

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:

1) Please provide clear information about the actual total number of individuals included in each of your comparisons, reporting by country. This could be done as a table or figure and could be part of your supplementary material. This could be the equivalent of your Figure 1 but for each comparison/cohort.

2) Regarding your Figure 1, please expand as to how the comparator group ‘gained’ 111,994 people as part of your matching strategy. Please expand on the matching strategy used in the paper.

3) Currently, the results reported are inconsistent, sometimes presenting on UK cohort, others for US, etc. Please give tables and figures for the estimates of each cohort that were included in your pooled estimates (Report the point estimates per database as well as the measure of heterogeneity for the pooled estimates). Your supplementary Table 7 makes clear that pooled estimates were only available for a handful of comparisons and from a subset of the cohorts. This needs to be reported better in your Results section.

4) The use of Random Effects or Fixed Effect Models should not depend on heterogeneity observed. Please adjust and present results based on a selected model while defending your choice. Sensitivity analyses are acceptable to check for robustness. Related, please provide estimates of heterogeneity linked to your pooled estimates.

5) Please be consistent in your reporting of effects. Your pooled estimates are only consistent with an effect of the AZ vaccine vs Pfizer on Thrombocytopenia. All other estimates are consistent with the null (e.g. the estimate presented for Janssen vaccination does not appear to be consistent with their interpretation). This might be due to lack of power which should be included in your discussion.

6) A novel aspect of your work could be to estimate the rate of these major adverse events in a reference group (e.g. Pfizer). Assuming that this vaccine is not associated with an increased risk, it might be possible to refer to this as a baseline risk and estimate this for some of your age subgroups or at least by country (taking into account the age distribution of those present).

7) The names of the vaccines are confusing and difficult to follow through the paper. Please consider changing them back to the generic names, or providing a box early in the paper with information on these.

8) It’s disappointing that it only looked at a small piece of the picture. There is no comparison with thrombotic events from covid-19 itself, no breakdown into age groups and no analysis on the booster dose.

9) It seems to assume the individual receives the same vaccine for 2nd dose. What if they received a different 2nd vaccine?

10) This is still of interest but may be mostly of historical interest by now. Could the primary message be made clearer?

11) The calibrated IRR is sometimes confusing. For example, sometimes the IR is higher than the reference group but the calibrated IRR is <1 (e.g. the IR for Thrombocytopenia in CPRD >> the IR for Vaxzevria 2nd dose was higher than the Comirnaty 2nd dose, but the calibrated IR is <1). The original article on calibration (Ref# 31) talks about calibration of p-values, not of IRR.
12) The background rates also varied in these databases, which the authors have reported before (BMJ 2021;373:n1435). Therefore, it would require a more elaborate discussion as to whether (i) the background risk had any impact on the effect estimates, and (ii) if it was appropriate to pool the effect estimates.

13) How do the rates in this study differ from those reported elsewhere, say, in BMJ 2021;374:n1931?

14) The number of events were small for individual outcomes and a 30% higher risk may mean very different risk based on the baseline rates. So, it would be more appropriate to report absolute risk differences, particularly by number of vaccines administered.

15) It’s not clear (especially for non-methodologist readers) what “Comparisons were limited to those with sufficient statistical power” means.

16) The quality of databases is worrying. Table 1 shows the 7 databases have varied data quality and completeness, with only 2 having complete vaccination data and 1 having linked hospital treatment and outcome information (thus the capture of outcome events might not be complete).

17) Some important covariates are missing from PS matching, e.g. race/ethnicity, SES, BMI, smoking, etc, and since most covariates were extracted from medical records, their completeness and validity depends on the quality of the database.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:
I read with interest this study. I commend the authors for their efforts. The study is very well conducted and in general I have no major comments and only 2 minor ones.

The first comment I have refers to the reported incidence rates for events (e.g. Line 282) that could be misleading to some readers if they remain reported as IR per 1000 person-years. I wonder if it would make more sense to report them in person-weeks (although not very common) or in 28-day IR as the losses to follow up are likely to be low given the short time frame. Please emphasize that the risk refers to people receiving one vaccine versus another and not to the risk associated with the vaccines per se. In fact, to highlight the overall safety of the vaccines it may be helpful to report the incidence per doses administered. I strongly suggest you include this information.

Additional Questions:
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Reviewer: 2

Recommendation:

Comments:
This paper is a detailed and comprehensive analysis examining risks of thrombosis associated with four different Covid-19 vaccines, combining results from large health databases from a number of European countries and the US. It is a major strength of the study that it was conducted across multiple countries and examined four different vaccine types (first and second doses only).

Negative control outcomes – these are a useful addition and add to robustness of the current research.

Key points
The authors should highlight more clearly what their research adds to the published literature as several papers reporting large observational studies have now been published on this topic, and it is unclear how their results compare with these other studies and whether their paper adds enough to what is already in the published literature.

Covariates: Justification is needed for the selection of these covariates. Some are quite vague e.g. "medical history any time before cohort index" and further detail is needed.

Several published articles to date have shown differences in risks associated with vaccines between younger and older people (e.g. Andrews NJ, et al. Lancet Regional Health-Europe. 2022 Feb 1;13:100260.; Whiteley WN, et al. PLoS medicine. 2022 Feb 22;19(2):e1003926). In the current paper it would be helpful to have additional analyses in age/sex sub-groups.

The statistical analysis section needs to explain how missing data were addressed and how loss to follow-up was addressed in accordance with STROBE.

Figure 1 shows that a lot of people were dropped from the target population due to not being matched on propensity score, so the final numbers included in analyses are much smaller than those listed in the Abstract and the first paragraph of the Results. These final numbers for all vaccine comparisons should be included in the Abstract and in the main paper. The potential impact on results of dropping such large proportions of vaccinated individuals and on external validity/generalisability needs to be discussed.

The Results section is very detailed and quite complex to read and identify the key findings. It would be clearer if it presented the overall meta-analysis results and described any heterogeneity between countries as it is not easy to tell from the results whether there were consistent findings between countries.

The results are only reported in terms of relative rates but absolute and excess rates over 28 days post vaccination (e.g. per 1,000,000 vaccinated) would be informative and help with risk communication.

Lines 347-348. The study from Scotland (ref 13) is rather cursorily dismissed in general terms which do not capture the main arguments in ref 37 or the related correspondence or specific features of the Scottish study, and it should be noted this study also included a self-controlled case series analysis.

Table 1 indicates incomplete data on vaccines and outcomes for some of the databases. This is a major limitation which needs further discussion in terms of likely impact on results. The limitation stated for detection of TTS (lines 384-388) is a major one.

Paragraph in lines 389-395. It would enhance the paper and interpretation of results to give some information on the vaccination policies and approval dates in each country including which specific vaccines were recommended in which population groups. It should be noted that after propensity score matching to balance cohorts some of the higher risk groups might be excluded. It is also important given that as stated here the most vulnerable were vaccinated with the first vaccines approved that calendar time is accounted for and well balanced in the comparisons between vaccines, this needs to be stated more clearly in the results and emphasised here.

Lines 347-358. More direct comparisons with the previous literature in terms of magnitude and precision of effect sizes are needed.

Discussion of clinical and policy implications of the research findings is needed.

Minor comments:
Specify in Methods (line 137) what the age inclusion criterion was.
Justify on line 153 why a 28 day exposure period was used.
There are a large number of primary outcomes, or were some considered as secondary outcomes?

Lines 207-208: Sentence about MDRR is unclear – what was the statistical power used for these calculations?

Line 210 - <20% of what?

Line 213 – give some more detail for the Poisson regression. Did it account for the propensity score matching? Was an offset term included and how was it defined?

Line 214. Empirical calibration is only described in very general terms. Further description is needed about how it works and explaining that it used the results for negative control outcomes.

Line 330. The first sentence of the discussion should be removed. In a rapidly evolving area it is unclear whether the knowledge of the authors is based on a recent literature search. Also whilst this study was designed to give a direct comparison other published real-world studies allow indirect comparisons. Numbers should be added to Tables 2-4.

Additional Questions:

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If you have any competing interests please see BMJ policy</a> please declare them here: I also am employed by the University Oxford as a senior researcher.

I have previously been a paid consultant statistician for ClinRisk.


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Reviewer: 3

Recommendation:

Comments:
This article compares the risk of thromboembolic and thrombotic events with thrombocytopenia in people vaccinated with different types of COVID-19 vaccines – mRNA vaccines (Comirnaty and Spikevax) and adenovirus vaccines (Vaxzevria and Janssen COVID-19 vaccine). The authors gave enough background and were clear about their objectives. The findings are similar to other studies the authors cite (basically, COVID-19 adenovirus vaccines increase the risk of thrombosis with thrombocytopenia syndrome when compared to mRNA vaccines). This work is highly important for informing decisions regarding which COVID-19 vaccines should be prioritized. The paper's strength is the big number of people included resulting from the network composed by six countries. Overall, the writing was clear as grammatically correct. Some questions the authors might consider:

1 - Please consider "COVID-19" instead of "covid-19", as abbreviations should be written in capital letters. This is how the World Health Organization uses the abbreviation.
2 - In line 50, please consider using "was" instead of "being" to make it a phrase.
3 - There's a typo in line 165, please consider "myocardial infarction" instead of "myocardial infraction".
4 - In methods section, you describe mostly primary care databases. Is information from hospital's visits available in those databases? If information from hospitals is not used, many thrombotic events may be missing in your database.
5 - Regarding covariates, how was "medical history any time before cohort index" included in the propensity score? Can you please describe with further details and objectively the covariates used?

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