Dear Editors,

We hereby submit a second revision of our manuscript BMJ-2022-071594.R1, entitled “The comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines: an international network cohort study from five European countries and the US”

We have carefully considered all comments from the statistical reviewer, and responded to each of their queries in a point-by-point response below these lines. We believe that this process has enhanced our manuscript, and hope that our clarifications and modifications will be satisfactory.

We look forward to hearing back from you in due course.

Yours faithfully,

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** Comments from statistical reviewer**

Comments:

Stats Report:
The authors present an international study based on multiple cohorts, mainly obtained through electronic health records, from the UK, France, Germany, Spain, the Netherlands, and the US, to carry out a comparison of the risk of thrombosis following different types of COVID-19 vaccines (ChAdOx1, BNT162b2, Janssen, and mRNA). They have used multiple state of the art approaches aiming to minimise the potential bias that arises from the use of observational data when carrying out comparative effectiveness. In particular, they use L1 regularised logistic regression to carry out their PS matching, they ensure power in each cohort to carry out a valid comparison (including only results that are based on more than one cohort), and finally they use negative controls to further validate and calibrate their effect estimates. These are all useful and valid approaches, nevertheless, their conclusions do not appear to be based on this strategy. In particular, their conclusions regarding Janssen (Ad26.COV2.S) are based on results from a single cohort that did not appear to provide adequate negative controls (based on their own analysis strategy and results presented in Table 5). Hence, the manuscript requires some critical adjustments/clarifications before publication in the BMJ could be recommended.
RESPONSE:

We would like to thank you for the detailed review of our manuscript. We have revised the manuscript accordingly. We have now re-organised our Results section focusing on the pooled results and reported database-specific estimates only where these met all the prespecified diagnostics. We have also revised related sections and statements accordingly.

We want to clarify that the observed borderline risk for Ad26.COV.S was obtained from a meta-analysis of Spanish and US data, rather than from US data alone. As per our protocol, meta-analytic estimates included database-specific estimates if they fulfilled the covariate balance (observed confounding) diagnostic, even if they did not fulfil the power diagnostic (MDRR<5). For this specific analysis, we have clarified in the revised manuscript that data from Spanish SIDIAP and US Open Claims was used to obtain these meta-analytic calibrated estimates. This is also now evident in our revised version of Figure 2.

This is the revised text that describes this finding in the Results section:

“Thrombosis-thrombocytopenia (TTS) was very rare, and could only be analysed in UK data for ChAdOx1 and in US and Spanish data for Ad26.COV2.S. A borderline significant increased risk of TTS was observed in UK CPRD following either 1-dose ChAdOx1 vs 1-dose BNT162b2 (calibrated IRR 1.29 (0.94 to 1.77)), but not after second dose (calibrated IRR 1.16 (0.71 to 1.89)), and not replicated elsewhere. As for Ad26.COV2.S comparing with BNT162b2, meta-analyses were possible for TTS-VTE and TTS-DVT. A borderline statistically significant but clinically relevant increase in risk was seen for TTS-VTE in the meta-analysis of US and Spanish data (pooled calibrated IRR 2.26 (0.93 to 5.52)), with much more uncertainty for TTS-DVT (pooled calibrated IRR of 1.83 (0.62 to 5.38)), see Figure 2. Database-specific estimates from US Open Claims were in line with the pooled results. (Table 5).”

We have carefully reworded this finding and put it in context with previous existing knowledge in the Discussion section of the manuscript as follows:

“Thrombosis with concomitant thrombocytopenia was very rare, and we did not find any statistically significant increase in risk with either adenovirus (compared to any mRNA-based) vaccine. However, this finding needs to be put in context with previous research, as some of our estimates were borderline significant, suggesting a potential increased risk of TTS-VTE with Ad26.COV2.S. While both thrombosis events and thrombocytopenia have been studied as separate outcomes, TTS was barely studied as an individual outcome in previous real-world studies due to the complexity of the case definition and rare nature of the outcome in case definition.[39] A US case series using the Vaccine Adverse Event Reporting System estimated rates of TTS were 3.83 per million vaccine doses of the Ad26.COV2.S and 0.00855 per million vaccine doses of mRNA-based covid-19 vaccines[40]. Yet the authors stated that TTS cases reported after mRNA vaccines are among different demographic characteristics and medical history compared to cases after Ad26.COV2.S. In comparison, we used routinely collected health data and were able to estimate the comparative risks between vaccines, therefore minimising surveillance bias.”

Finally, and to avoid any confusion in the readership, we have clarified that our limited power was a limitation for the analysis of TTS in the Limitations subsection of the revised paper:

“Finally, and despite the use of large international data sources, we had limited power for the analysis of TTS, a rare event, resulting in only three databases (UK, Spain and the USA) contributing to our findings. In addition, meta-analysis was only meaningful for the analysis of Ad26.CoV.S, and resulted
in wide confidence intervals and borderline (not statistically significant) estimates. These analyses therefore warrant replication elsewhere.”

Major issues:

The following statement: ‘Our international analysis allowed us to analyse both adenovirus-based vaccines to confirm TTS as a potential class effect.’, is misleading as none of your estimates for the Janssen vs. other comparison is significant for this outcome based on the uncalibrated analyses (the calibrated analyses do not pass the authors’ own requirements set). The same applies for the effect for this outcome on ChAdOx1 vs. BNT162b2. Again, this is only reported in one database. The Results need to be re-written based on this and this will also affect the main conclusions (including Abstract) and the ‘What this study adds’.

RESPONSE:

We have removed the mentioned sentence from the revised manuscript. Instead, we have focussed on results from pooled estimates and database-specific estimates that passed all our pre-defined diagnostics. We have also revised the Abstract, Results, Discussion sections, and the summary box accordingly.

Reference 31, Tian et al, presents a simulation study comparing L1 regularized logistic regression vs. high-dimensional propensity score (hdPS) and find that in some scenarios L1 outperforms hdPS. This is not the same as saying that this approach will be better than any situation where the covariates to be included in the PS are identified (by experts or otherwise). Please correct this mention in the Methods section as this could generate incorrect analyses going forward.

RESPONSE:

We agree with the reviewer and have revised the Methods section as requested.

The lack of some important confounders in some of the datasets is still a mayor limitation. This will need acknowledging in the Discussion. The use of negative control outcomes and their role here to identify potential unmeasured confounding is therefore particularly relevant, and so are the calibrated estimates presented (hence the reason for the Janssen results being particularly problematic).

RESPONSE:

We agree that we see evidence of unmeasured confounding in the US Open Claims database, and have used empirical calibration to reduce the potential resulting bias. In the revised manuscript, we haven’t reported uncalibrated results to avoid misleading the readership. Additionally, we have expanded our text on the limitations related to unmeasured confounding.

As there are no results reported for the LPD France and US Hospital CDM, it would be worth mentioning this in the Results as it currently gives the wrong impression that the conclusions are
based on all countries/datasets. Similarly, need to decide if the fact that calibration was not possible in the IPCI and Germany DA means it should also be included in the results. It seems to me that the results really rest on the data from UK, Spain and one US database.

**RESPONSE:**

US Hospital CDM failed the covariate balance diagnostic after the propensity score matching, and hence no data from this database was reported. Regarding France LPD (1st dose ChAdOx1 vs BNT162b2), covariate balance was reached with all covariates had SMD below 0.1 after propensity score matching. No database-specific estimate was reported due to limited statistical power (based on MDRR-related diagnostics), but estimates for some outcomes (where MDRR<5) contributed to the meta-analysis. Finally, we included all comparisons where covariate balance was reached into the meta-analyses. Pooled results were estimated and calibrated as well. We have clarified this in the Results section. We also added the plots of systematic errors for the meta-analyses in Supplementary Figure 3.

In the Comparative safety section, the authors write ‘Seven outcomes were estimated in more than one database, and therefore included in meta-analyses.’ However, in Figure 2, there are 11 outcomes for the Janssen COVID-19 comparison. In Table 5, there does appear to be only 7 outcomes for the Janssen COVID-19 comparison with 2 or more studies reporting but this does not correspond to Figure 2.

**RESPONSE:**

Based on our pre-specified statistical analysis plan, the meta-analyses was due to include database-specific estimates regardless of statistical power (not requiring MDRR below 5). Conversely, we only aimed to report database-specific estimates with sufficient power (MDRR<5), and this is what we reported in Table 5. Therefore, the reviewer is right that there is a mismatch, as meta-analyses included outcomes that did not meet the pre-specified MDRR threshold, including SVT, intestinal infarction, TTS-DVT, and TTS-VTE. The statement “Seven outcomes were estimated...” was meant to describe the comparison of first dose ChAdOx1 and BNT162b2, but we understand this was misleading. We have now clarified this in the revised manuscript. We have also modified Figure 2 to more clearly illustrate the databases included in the reported meta-analyses to avoid confusion.

Regarding this last point, in Table 5, there is a mention that only the ChAdOx1 vs. BNT162b2 comparison met your criteria for minimising bias (1st dose and 2nd dose too). I imagine this is the reason only these are included in the Results section. If that is the case, all the other results for the other comparisons, should only be included as supplementary material and not in the main Results.

**RESPONSE:**

In our analysis, while the comparisons between Ad26.COV2.S and two mRNA vaccines in the US Open Claims showed systematic error, the estimates were corrected after empirical calibration as specified in our protocol. For BNT162b2 and mRNA-1273, there were 27.8% and 32.1% of the negative control outcomes associated with the exposure before the calibration, but only 5.1% and 9.0% remained associated with the exposure after empirical calibration, illustrating the value of this calibration strategy (see supplementary figure 2). Therefore, we only reported the calibrated
estimates in the Results section of the revised manuscript. We have also emphasised in the Discussion of the revised manuscript that only the calibrated results should be interpreted.

Figure 2: What is presented in the second column? Is this the I2? Please label. In the same Figure, please include the studies reporting on these outcomes. This could be as a simple label for each comparison.

RESPONSE:
Thank you for the suggestions. We have labelled the column of I2, and added an extra column specifying the databases included in each meta-analysis. We hope this revised version of Figure 2 will be clearer to the reviewer and subsequently to the readers of our paper.

Minor issues:

Do the IQVIA hospital charge (US) and the US Open Claims datasets have some overlap or are they completely separate populations? If there is overlap, this might have generated some bias (even if the Open Claims dataset analysed was only a 20% sample of the total). If there is substantial overlap, one alternative is to do a sensitivity analysis excluding one of the US databases (this is not an issue as this is not included in any analysis but would be useful to have a comment in the Discussion).

RESPONSE:
The reviewer raises an important point regarding the potential overlap of study participants in the two included US databases. However, US Hospital CDM data was not included in any of our analyses due to a failure to pass our pre-specified covariate balance diagnostic. We can therefore reassure the reviewer and editors that no further analyses were conducted or reported for this data source. We hence know that any overlap between both databases is no longer a concern, as only Open Claims was used for exposure-outcome analyses.

Please check definition in sensitivity analysis. Likely there is a typo (before OR after?): “1. Requiring the concurrent thrombocytopenia happened within 5 days before of after the thromboembolic event after vaccination.”

RESPONSE:
We have corrected this in the revised manuscript.