Exhibit 619

Batch-dependent safety of the BNT162b2 mRNA COVID-19 Vaccine

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LETTER TO THE EDITOR

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To the Editor:

In the aftermath of our recent research letter that suggested a batch-dependent safety signal with the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech),[1] concerns have been raised in the journal about the methodology and interpretation of the data.[2–4] As was explicitly stated in our letter, the results were hypothesis-generating and not usable to infer causality. Unsurprisingly, however, the study received massive public exposure, especially on social media platforms, with responses ranging from unreserved acclamation to obsessive criticism[5] whereas new formal peer-reviewed BNT162b2 mRNA vaccine batch-dependent data have yet not become available. Against this background, we here briefly address some of the principal points that were rasised.[2–4]

First, as stated in our report,[1] spontaneous (or passive) adverse events reporting systems like the US VAERS and the system managed by the Danish Medical Agency (DKMA) used in our study carry inherent limitations, for example, underreporting, and incomplete and inaccurate data.[6,7] Notably, unlike VAERS, SAEs reported to the DKMA are reviewed and processed by the DKMA before their public release. The WHO VigiBase is subject to similar limitations as VAERS and the relevance of the worldwide study of suspected adverse events (SAEs) reported to VigiBase with BNT162b2 and Moderna mRNA vaccines compared to conventional influenza vaccines that was highlighted by one respondent[2,8] for our study of BNT162b2 batch-dependent safety in Denmark is unclear to us. Furthermore, our study was based on reported SAEs from 13,635 subjects and such substantial population-based sample renders underreporting (if consistent between vaccine batches) less important. As inferred by a respondent from the Danish Statens Serum Institut (SSI),[3] on June 24, 2021, the DKMA issued a press release that requested for people to not report simple and transient SAEs. This request, however, was not linked with a noticeable concomitant drop in reported SAEs and our current data show that use of the blue trendline batches was completed by mid-March 2021, indicating that the DKMA request did not contribute to the highly significant reduction of SAEs/1.000 doses observed between the blue and the green trendline batches (figure 1 in our report).[1]

Second, at the time of submission of our report we had been denied FOI access to temporal data from the SSI which is responsible for vaccine safety in Denmark, and we were hence unable to meaningfully speculate about the apparent 'zero SAE' yellow batches that are questioned by the respondent from the SSI.[3] However, after publication of our report it became apparent in public statements made by the SSI that these batches were the last batches used during the study period and that the alphanumeric order of batch identification codes did, in fact, reflect their temporal order of use. Accordingly, the blue, green, and yellow trendline batches were the first, second, and last batches to be used, respectively, and the most likely reason for 'zero SAE' batches was a backlog of unprocessed SAE reports present at the DKMA at the time of our data retrieval. A subsequent inclusion of this backlog in our analyses indicates that the slopes of the green and yellow batch trendlines increased slightly, that is, the 'zero SAE batches' disappeared, but that the overall trends presented in figure 1 of the report[1] were relatively unchanged (own unpublished results). Regarding shipped vs. administered batches,[2,3] the batch size data that we received from the SSI were presented to us by the SSI as 'number of doses per batch, that have been delivered and used in Denmark'. Although this would appear to assume complete 100% usage of all shipped vaccines, we compared these data to the total number of administered vaccines on the precise cut-off time of data retrieval that was displayed on the Danish vaccine dashboard that is managed by the SSI and we found only a $<0.15\%$ difference between the number of shipped and administered doses. Accordingly, after having also checked that no vaccine batch (in part or as a whole) remained stored at the SSI warehouse was included in our data, we reported doses as being the number

of 'administered' doses, since the phrase 'shipped doses' would lead readers to wrongly think that the reported number of doses per batch differed significantly from the number of administered doses per batch.

Third, since we had been denied access to temporal data by the SSI, we were unable to explore whether the high SAE blue trendline batches were administered at the start of the vaccine rollout, but as indicated above this was confirmed publicly by the SSI after publication of our report. However, the notion that high SAE batches in our study was a result of these batches being administered to old and frail subjects at the start of the vaccine campaign disregards that these individuals are not those most likely to report their SAEs and they were vaccinated not only twice at the start of the vaccination campaign, but once again hereafter during the early campaign period, and then again from mid-September 2022. These consecutive revaccinations should likely then have given rise to a substantial lift in SAEs from batches used in the later study periods, that is, the green or yellow batch trendlines.[1] Yet no such lift was observed, but rather a steady decline over time in rates of batch-dependent SAEs pr. 1000 doses. Moreover, younger front line health care workers were, of course, also among the first to be vaccinated. We have now gained access to data on the age of subjects with reported SAEs and for the high SAE batches (report's figure 1, blue trendline),[1] only 21% of SAEs were reported in people ≥70 years, while this ratio was 22% for 'medium SAE batches' (green trendline) and 27% for the 'low SAE batches' (yellow trendline), respectively. Therefore, it appears highly unlikely that selective administration to old and frail persons during the first phase of the pandemic was a primary contributor to the emergence of the apparent high SAE batches. Notably, a potential for vastly increased risk of SAEs in elderly and frail persons is not mentioned in the summary of product characteristics for the BNT162b2 vaccine.

Fourth, regarding the comment from the respondent from the SSI about our use of non-hierarchical cluster analysis methodology,[3] it was clearly apparent from the x-y plot (report's figure 1)[1] that the relationship between numbers of SAEs and BNT162b2 vaccine doses in different batches was highly heterogeneous. Therefore, conventional linear regression statistics were not considered readily applicable. Furthermore, standard methods for examining heterogeneity in linear models, for example, latent class analysis[9] and finite mixture modeling[10] did not yield usable results, likely because the discriminatory ability of these models is markedly reduced when regression line slopes approach zero (report's figure 1, yellow trendline).[1] Accordingly, we applied a more robust strategy by use of the simple fact that any plausible trendline must pass through origin (0,0) as there are invariably 0 SAEs with 0 doses. Therefore, the trendline for each single vaccine batch was characterized by the equation 'y=β * x', where y was number of SAEs per batch, x was number of doses per batch, and β was the slope of the individual batch trendline, respectively. By isolating 'β', nonhierarchical cluster analysis could be applied to the vectors of all 'βs' after log transformation, since 'β' showed a roughly exponential distribution and vectors were hereby segmented into three clusters with maximized homogeneity within trendline clusters, as well as maximized heterogeneity between these clusters, respectively. Hereafter, analysis of variance (general linear model [GLM]) was performed between the three trendline clusters as groups and showed significant differences ($p < 0.0001$) between the groups as reported in our letter.[1]

Fifth, other respondents have claimed that Poisson GLM should have been used to connect the linear model to the nonlinear response variable representing SAE counts per 1.000 doses and that the choice of the three clusters should have been justified.[4] However, as described above we did not use the GLM directly on the count data but performed a nonhierarchical cluster analysis followed by Poisson GLM test on the β value for each batch. The latter variable is theoretically a linear continuous variable that is suitable for both GLM and cluster analysis. Also, it is notable that nonhierarchical cluster analysis does not contain any mechanism for determining the optimal number of clusters. Indeed, this deduction is often done (as we did) by first using hierarchical cluster analysis. The presence of three clusters was clearly apparent in figure 1 of our report and the GLM tests revealed that this solution provided statistically significant separation of the batch profiles.[1]

Finally, after publication of our report, we have become aware of the first Periodic Safety Update Report (PSUR) for the BNT162b2 vaccine covering the period 19 December 2020 to 18 June 2021 that was submitted to the European Medicines Agency on 19 August 2021 by the market authorization holder (BioNTech).[11] This PSUR appears to confirm a large variation in numbers of adverse events between different BNT162b2 batches and batches with the highest number of adverse events reported here were all those represented by the blue 'high SAE' trendline in the figure of our published study.[1,11]

In conclusion, the preliminary findings in our report emphasize that the results are hypothesis-generating and cannot be used to establish causality.[1] We eagerly await more definitive studies of batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine, for example, from the SSI, to refute or validate our results and increase the evidence base for this important area of research.

CONFLICT OF INTEREST STATEMENT

None.

Max Schmeling[1]
Vibeke Manniche[2]
Peter Riis Hansen[3,4]

[1]*Innometric, Skørping, Denmark*
[2]*LIVA, Copenhagen, Denmark*
[3]*Department of Cardiology, Copenhagen University Hospital—Herlev and Gentofte, Gentofte Hospitalsvej, Hellerup, Denmark*
[4]*Faculty of Health and Medical Sciences Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark*

Correspondence
Peter Riis Hansen, Department of Cardiology, Copenhagen University Hospital —Herlev and Gentofte, Gentofte Hospitalsvej, Hellerup, Denmark.
Email: peter.riis.hansen@regionh.dk and prha@sund.ku.dk

ORCID

Peter Riis Hansen https://orcid.org/0000-0002-9056-535X

REFERENCES

1. Schmeling M, Manniche V, Hansen PR. Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine. *Eur J Clin Invest*. 2023;53(8):e13998. doi:10.1111/eci.13998 Epub 2023 Apr 9.
2. Del Saz BS. Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine. *Eur J Clin Invest*. 2023:e14050. doi:10.1111/eci.14050 Epub ahead of print.
3. Hviid A. Inaccurate representation of shipped vaccines as administered. *Eur J Clin Invest*. 2023:e14066. doi:10.1111/eci.14066 Epub ahead of print.
4. Scott DAR, Renelle A, Niederer RL. Methodological and statistical considerations: batch-dependent adverse effects of COVID-19 vaccines. *Eur J Clin Invest*. 2023:e14073. doi:10.1111/eci.14073 Epub ahead of print.
5. Prasad V, Ioannidis JPA. Constructive and obsessive criticism in science. *Eur J Clin Invest*. 2022;52(11):e13839.
6. Aagaard L, Stenver DI, Hansen EH. Structures and processes in spontaneous ADR reporting systems: a comparative study of Australia and Denmark. *Pharm World Sci*. 2008;30:563-570.
7. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the vaccine adverse event reporting system (VAERS). *Vaccine*. 2015;33:4398-4405.
8. Kim MS, Jung SY, Ahn JG, et al. Comparative safety of mRNA COVID-19 vaccines to influenza vaccines: a pharmacovigilance analysis using WHO international database. *J Med Virol*. 2022;94:1085-1095.
9. Asparouhov T, Muthén B. Residual associations in latent class and latent transition analysis. *Struct Equ Model Multidiscip J*. 2015;22:169-177.
10. Hair JF Jr, Sarstedt M, Matthews LM, Ringle CM. Identifying and treating unobserved heterogeneity with FIMIX-PLS: part I– method. *Euro Bus Rev*. 2016;28:63-76.
11. Periodic Safety Update Report #1 for Covid-19 mRNA vaccine (nucleoside modified) (BNT162b2). Submitted to the European Medicines Agency on 19 August 2021, made publicly available in response to a Freedom of Information Act (FOIA) request from an anonymous reader and published by the Austrian science and political blog, TKP. https://tkp.at/2023/01/17/aerzte-tragen-die-verantwortung-bei-impf-schaeden-und-fuer-deren-meldung/. Assessed September 18, 2023