Critique and questions regarding "No batch related accumulation of suspected case reports on vaccination adverse events after COVID-19 vaccinations with Comirnaty" – a public statement from the Paul Ehrlich Institute issued on August 18th, 2023.

August 24, 2023

by Max Schmeling, Vibeke Manniche, and Peter Riis Hansen

The above public statement from the Paul Erlich Institute (PEI), raises some important questions about the validity of the PEI data. Specifically, as detailed below, the PEI study showed adverse reaction rates that were up to more than 7 thousand times higher than the rates reported in our Danish peer-reviewed study. The adverse event rates reported by the PEI are, in fact, so high, that they appear completely unbelievable and suggestive of a study flawed by design. According to the numbers reported by the PEI, one dose of Comirnaty yielded 4,35 adverse reactions in total which then included 9,62 serious adverse reactions, and this is, of course, logically impossible.

Furthermore, the reported range of batch sizes differed for all adverse reactions vs. for serious adverse reactions, respectively, which also would seem impossible. This leads us to conclude that the PEI results were likely due to methodological errors in the data collection and counting of vaccine doses in each batch. We speculate that the PEI exclusively counted vaccine doses from the batches that were registered in the app used for reporting of adverse events, instead of correctly using the total number of doses administered to the German population.

By selecting this method, the study result was determined in advance since the design invariably would provide a linear relationship between doses and adverse reactions as clearly demonstrated in the two plots that were presented by the PEI (see below). This would seem to constitute a fatal flaw in the PEI study that makes the study and any comparison with the Danish study (or other studies) irrelevant.

Background

In our published report "Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine" https://doi.org/10.1111/eci.13998 we showed a potential safety signal regarding the BNT162b2 mRNA vaccine (Pfizer-BioNTech). Highly unexpectedly, we found a significant and not yet explained heterogeneity in the data, which suggested that there were three types of batches with distinctly and statistically different adverse reaction profiles.

Critical appraisal of the Paul Ehrlich Institute study

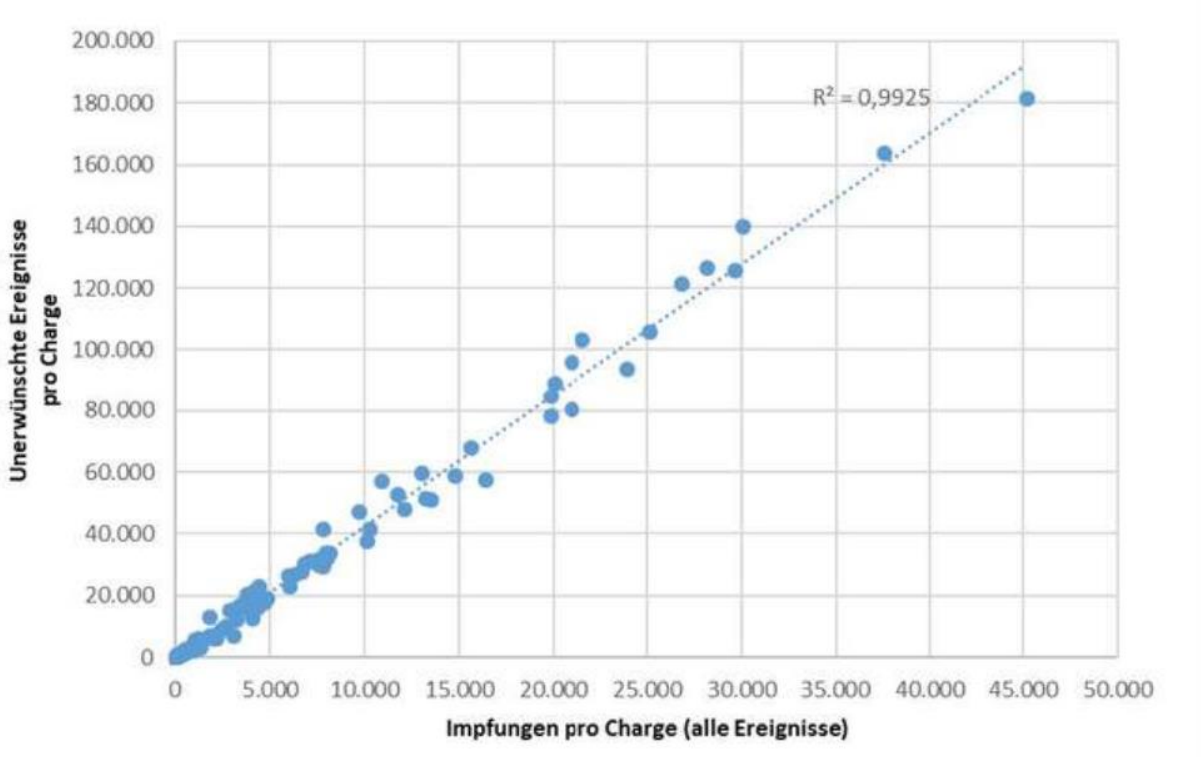
The PEI claims that a distinct linear relationship exists between doses per batch and number of adverse reactions registered per batch for both 'all adverse reactions' and 'serious adverse reactions', i.e., indicating that individual doses from all batches had similar rates of adverse reactions. The PEI data were collected by use of the SafeVac 2.0 app. Participants downloaded this app and registered by using their batch number(s) as a verification parameter.

According to the PEI data, for all adverse reactions, 244 different Comirnaty batches were registered related to 703.164 vaccinations which were associated with 3.061.920 adverse reactions. For serious adverse reactions, 137 different Comirnaty batches were registered related to 3.935 vaccinations, which were associated with 33.874 serious adverse reactions. For both all adverse reactions (R^2 [coefficient of determination] of 0,9925) and for serious adverse reactions (R^2=0,9924), the PEI data plots (see below) showed a homogenous and near-perfect linear relationship between dose numbers and adverse events, where for both models more than 99% of the variation in the data can be explained.

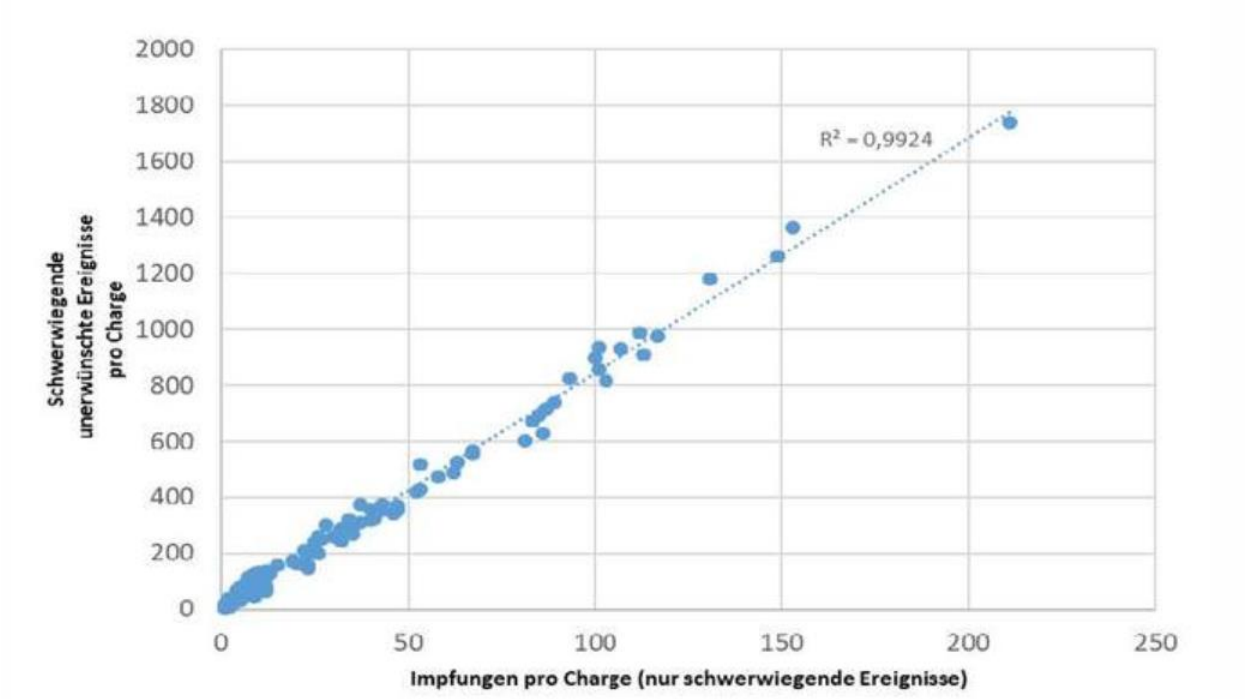
For all adverse reactions, the adverse reaction rate can be calculated as 3.061.920/703.164 = 4,35 adverse reactions per dose. For serious adverse reactions, the same calculation yields 33.874/3.935 = 9,61 serious adverse reactions per dose. This, of course, defies normal logic, since it is impossible within the same dataset to experience a rate of serious adverse reactions that is higher than the rate of all adverse reactions, given that the former is included in the latter.

For comparison, the data from our Danish study showed an adverse reaction rate for all adverse reactions of 0,0056 adverse reactions per dose and of 0,0013 per dose for serious adverse reactions. Regardless of any discussion of heterogeneity in the data, these results from Denmark are a magnitude of 777 and 7.392 times smaller, respectively, than the current results presented by the PEI. In practice, such enormous difference should be impossible since both the SafeVac 2.0 app data and the database of the Danish essentially measured adverse reaction rates for the exact same product.

The plot presented by the PEI were for <u>all adverse reactions:</u>



And for only <u>serious adverse reactions</u>:



These two plots allow for further observations. First, the distribution of the batch sizes (x-axis) is very heavy in the lower end of batch sizes, which is not consistent with an assumption of a reasonably equal batch size for all batches. This was not the case in the Danish study either, but in a much larger country as Germany (where larger size batches were generally likely to be used), this effect should be much smaller. Second, the range of the batch sizes (x-axis) is approximately 0 to 45.000 for all adverse reactions and 0 to 210 for serious adverse reactions. This seems extremely inconsistent, since individual batches should be of comparable size in both plots.

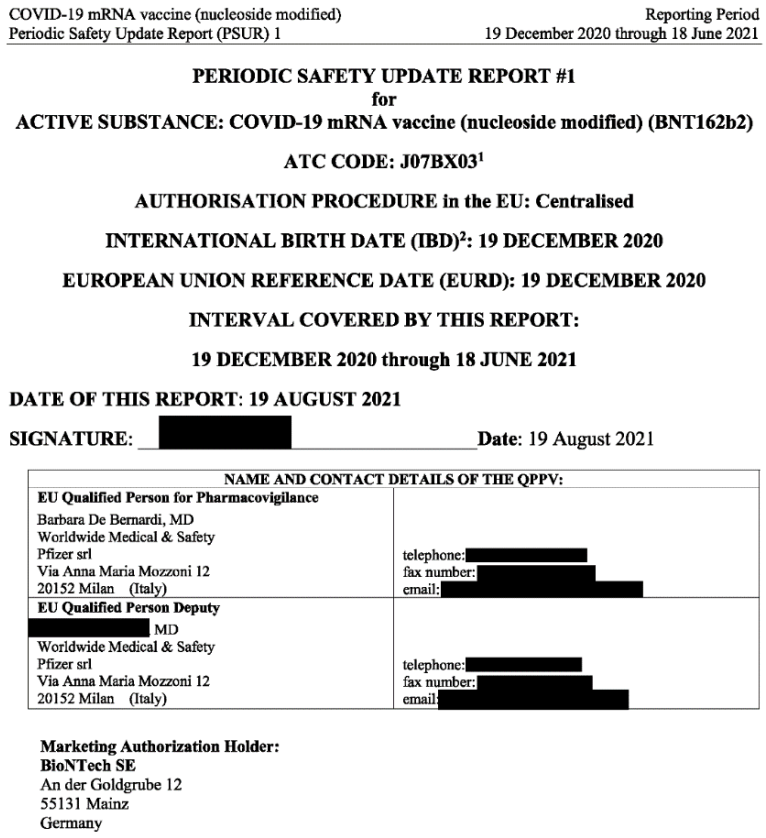
These unexplained and extreme differences between the PEI study and our Danish study are not reconcilable and we believe that the frameworks of the two studies were completely different. Although we are unaware of the exact methodology used in the PEI study, it seems clear from the enormous differences in adverse reaction rates between the Danish and the German data that the German batch sizes were limited and not representative of the total sizes of the administered doses per batch in Germany. Indeed, the differences and inconsistency in the ranges of the batch sizes (x-axis) in the two plots from the PEI presented above supports this assertion.

The only plausible explanation seems to be that the PEI used the number of adverse reactions registered by the SafeVac 2.0 app for the y-axis and the number of doses from individual batches registered in this app for the x-axis. According to the design of the study data retrieval, when a person registered her/his vaccine batch number in the app, this counted as one dose received from this specific batch and if this person registered one or more adverse reactions after vaccination with this batch, all these adverse reactions were counted as adverse reactions for this specific batch. However, this registration scheme does not take into account all the doses received by individuals with no adverse reactions since these persons likely did not register in the app. Indeed, this design aspect of the PEI data collection is consistent with the much higher

adverse reaction rate reported in the study compared to our Danish results, as well as the differences in the ranges of the batch sizes in the above two plots that were presented by the PEI, and the fact that the rate of serious adverse reactions reported by the PEI were more than twice the rate of all adverse reactions, respectively. However, omission of all or almost all the doses that did not elicit reports of adverse reactions in the PEI calculations would seem to entirely undermine the validity of the study and its conclusions. Indeed, if the above registration scheme was used in the PEI study, this methodology a priori generated a built-in linear relationship between the number of doses per batch and the number of adverse reactions, thus invariably leading to the highly homogenous linear trend between adverse events and number of doses per batch exactly as reported by the PEI.

In its public statement, the PEI was critical of our Danish study where we found significant differences in rates of adverse reactions between some batch groups, i.e., not the single linear relationship between adverse reactions and dose numbers for all batches that was reported by the PEI. As noted above, however, the flawed study methodology used by the PEI was predetermined to provide the results that were reported. To further demonstrate this fallacy, we have now applied the methodology used by the PEI to the Danish data and our results, as expected, were almost identical to those reported by the PEI (see Appendix).

In addition, it is notable that, the results from the PEI are highly inconsistent with the Periodic Safety Update Report (PSUR) that the European Medicines Agency (EMA) received from Pfizer-BioNTech:



COVID-19 mRNA vaccine (nucleoside modified) Reporting Period
Periodic Safety Update Report (PSUR) 1 19 December 2020 through 18 June 2021

PERIODIC SAFETY UPDATE REPORT #1
for
ACTIVE SUBSTANCE: COVID-19 mRNA vaccine (nucleoside modified) (BNT162b2)

ATC CODE: J07BX03[1]

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Marketing Authorization Holder:
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An der Goldgrube 12
55131 Mainz
Germany

Table 9. Most Frequently Reported Lot Numbers

Lot Number	Number of Cases
EL1484	16077
EJ6797	11168
EK9788	10139
EM0477	9214
EJ6136	7034
EJ6134	7029
EJ6795	7010
EJ6796	4942
EJ6788	4421
EL0725	3870
ER1741	3692
EJ6789	3136
EJ6790	2992
ER1749	2762
EP9598	2750
EL1491	2621
EJ3002	2602
EP9605	2461
EK1768	2157

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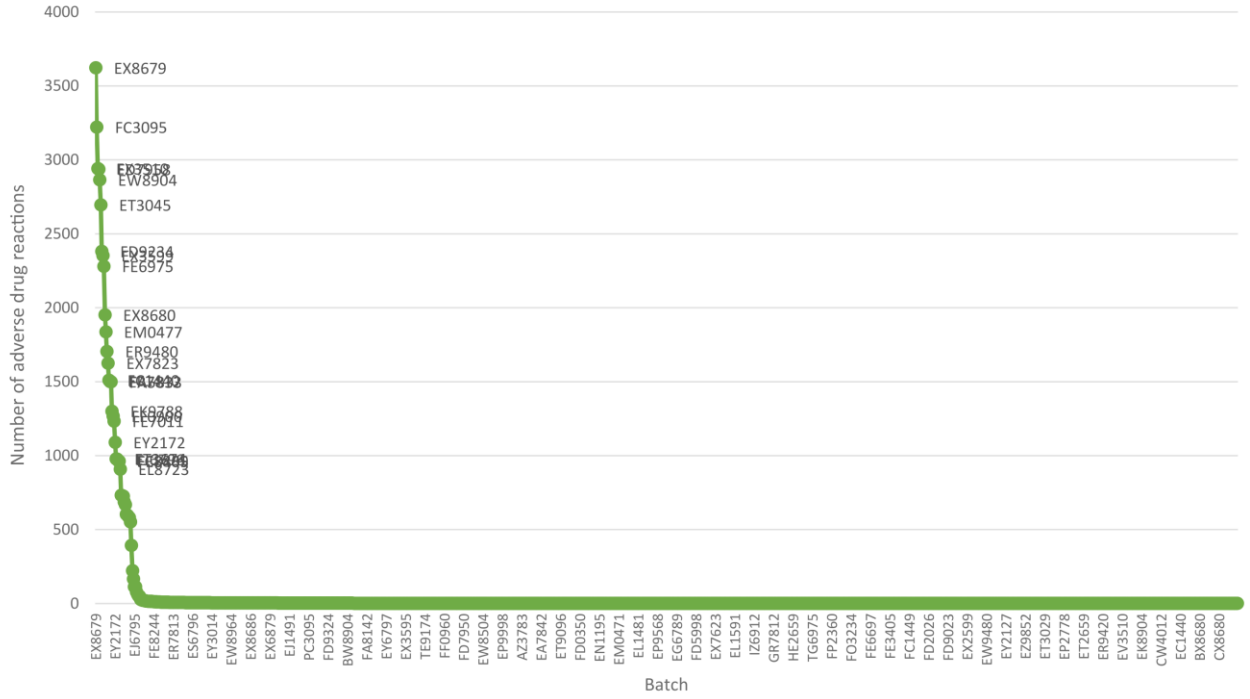
Table 9. Most Frequently Reported Lot Numbers

Lot Number	Number of Cases
EL8723	2154
EL0739	2133

This PSUR is available at:

https://cdn.website-editor.net/s/041bcc2c4aa54d419f7ee83c6c280b40/files/uploaded/21-08-19.PSUR1l.pdf?Expires=1693588209&Signature=NtoFNrcPd66PZC-btqPIBvLW~il0h0wK9B88MoYgiojNoi8qrhi9usPagLVdJOTVZpd0LVszWb8em3Zht426w0~4RSbwtYSlILf5BDGW~oFuAxzMiLdR0OE15lDoebedbAbgxOKZhp929IhIOvN3McWEpUEsdW7BrJXsZo7AvJpGWlFGqB52A-V8o8ynk31GMXyfN32eDlD374rcPRhZCj2UCVwI-URN15iHnKDLfeNJ3eK3g7B-5O0KqICW3oJYsBKeYEB3BDXo9bh9nocF5ysUnxJ0BeA7BbTt3gHjZifx0K1QwzEewMcsvAYBPNb79GkrgTTy2B4w2LL3k6HeKQ__&Key-Pair-Id=K2NXBXLF010TJW

The blue highlights in table 9 corresponds with the nine high adverse reaction rate batches in the blue batch profile presented in our Danish study. These data (Table 9, P56-57 in the PSUR) also clearly show a high level of heterogeneity between the number of adverse reactions per batch. Therefore, the current results from PEI are inconsistent even with the data that EMA received from the market authorization holder. Indeed, data from the EduraVigilance database that we have obtained through FOI request to EMA in March 2022 also show a similar heterogenous pattern in the number of adverse reactions per batch used in Germany (own unpublished results, see plot below).



Conclusion

We conclude that the PEI study appears to be flawed by design and the results of this study are contradicted by both our peer-reviewed Danish safety data and the safety data reported to EMA by the market authorization holder. We suggest that the PEI reconsider their data and we eagerly await peer-reviewed academic publication of the revised results from Germany.

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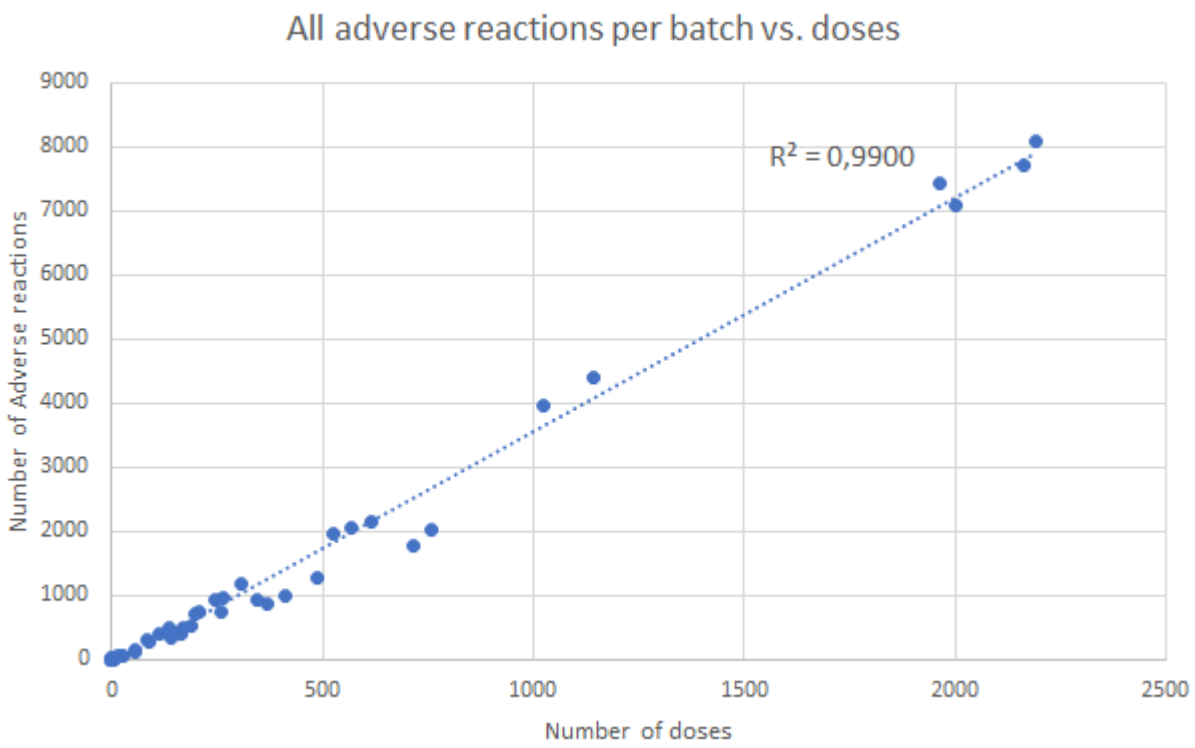
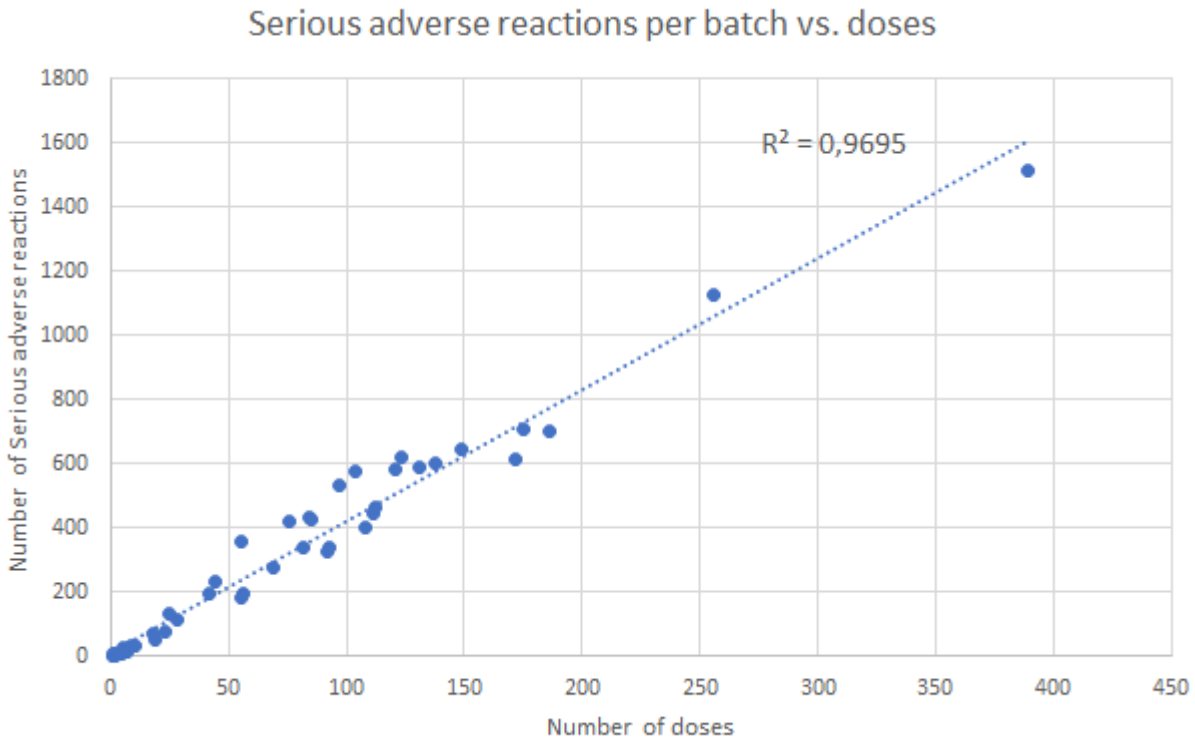
Appendix: A follow-up experiment with use of the Danish data

As outlined above, we suggest that the results presented by the PEI were caused by a flawed methodology, where the reported linear relationship between numbers of adverse reactions and numbers of vaccine doses was, in fact, specified a priori by ways of the PEI study design. Accordingly, it is implied that similar results may be obtained with other adverse reaction datasets using the same flawed methodology. We therefore applied the PEI study design on the data used in our Danish study to demonstrate that similar (but flawed) results could be obtained.

Methodology and Results

In the Danish dataset used in our published study, we used the PEI methodology and first counted all adverse reactions for each vaccine batch. We then counted all distinct individuals associated with each batch to obtain a surrogate for the number of administered doses. We then plotted these data with the number of doses on the x-axis and number of adverse reactions on the y-axis for each individual batch. We did this for 'All adverse reactions' and for 'All serious adverse reactions', respectively, and the results are showed in the two plots below.





Comment

These results are strikingly similar with those reported by the PEI, with the same strong linear relationship between numbers of doses and adverse events for all vaccine batches. However, as also discussed in the first part of our current critique of the PEI study, the results are caused by wrongfully using the number of respondents who reported adverse reactions as a surrogate for the number of administered doses. Indeed, this design creates a synthetic linear relationship between the number of doses (respondents who registered adverse reactions) and the number of adverse reactions experienced by these same respondents.

With use of the PEI methodology, we also calculated that the rates of adverse reactions for our dataset were 3,41 adverse reactions per dose and 4,31 serious adverse reactions per dose, respectively. Again, these results are strikingly similar with the results reported by the PEI, albeit that they remain logically impossible.

To summarize, application of the PEI study design to the Danish data clearly demonstrates that this design is set to determine the results in advance and that such results are therefore not scientifically valid.