# 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.

by Max Schmeling, Vibeke Manniche, and Peter Riis Hansen

The results presented in the above 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, they appear completely unbelievable suggesting the study could be 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, even though this is, of course, logically impossible.

Furthermore, the reported range of batch sizes differed for all adverse reactions versus for serious adverse reactions, respectively, which also would seem impossible. This leads us to conclude that the PEI's results were almost certainly due to methodological errors in the data collection and counting of vaccine doses in each batch. We speculate that the PEI counted vaccine doses according to the number of batches that were registered in the app that was 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 design introduced a synthetic and illusory relationship between doses and adverse reactions as clearly demonstrated in the two plots that we present 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 Poul Ehrlich Institute study

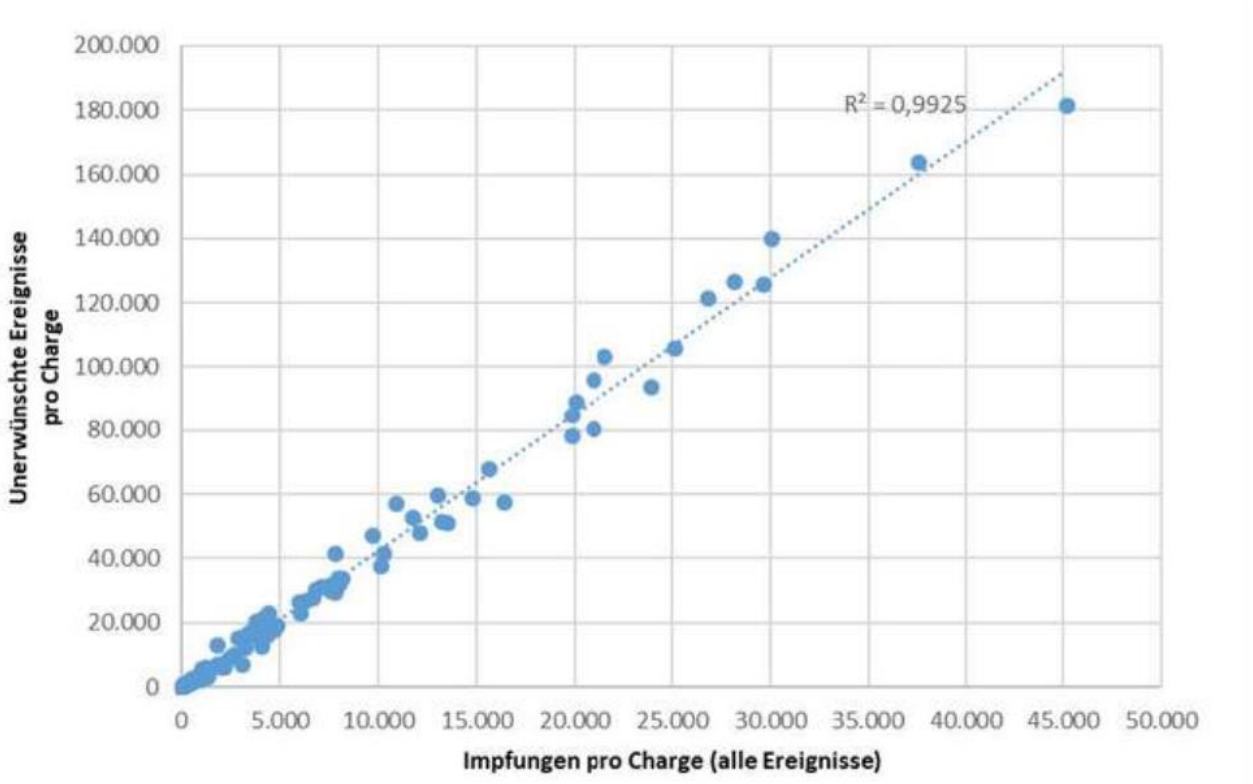
The PEI claims in their statement that a singular linear relationship exists between doses per batch and number of adverse reactions registered per batch for both 'all adverse reactions' and 'serious adverse reactions'. The data were collected by use of the SafeVac 2.0 app. Participants downloaded this app and registered by using their batch number(s) as a verification parameter. Notably, the use of an app for data collection introduces a data collection bias, e.g., with lower reporting rates for the elderly, and this bias may be stronger than with use of a simple web-based collection as is done in the official adverse reaction reporting systems, e.g., in Denmark.

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 ($R^2$=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.

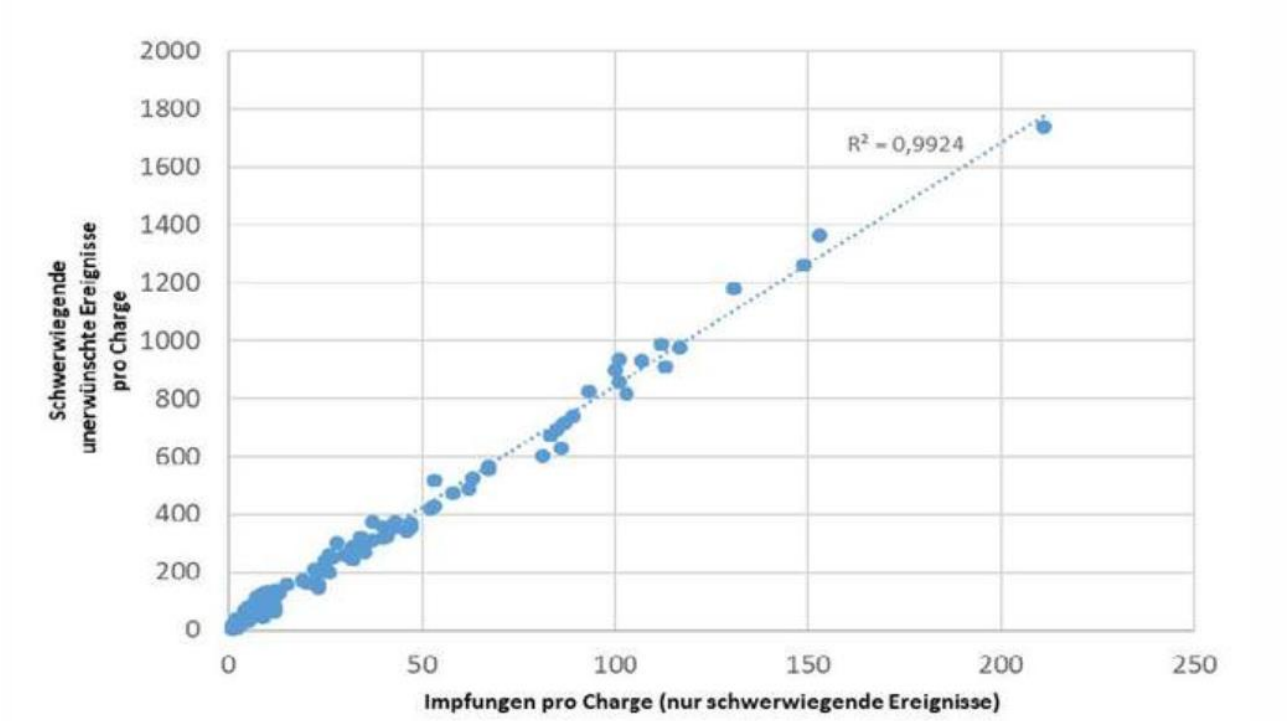
For all adverse reactions, the adverse reaction rate can be calculated as 3.061.920/703.164 = 4,35 adverse reactions per dose. For serious adverse reactions, the same calculation yields 33.874/3.935 = 9,61 serious adverse reactions per dose. This, of course, seems contrary to normal logic, since it is 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 event 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 the 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, this effect should be much smaller. Instead, it seems larger. 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 the same 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 as the y-axis and the number of batches registered in SafeVac 2.0 for each batch number as the x-axis. According to this scheme, if a person registered their batch number in the app, this counted as one dose from this specific batch number and if the same 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. The scheme would conversely not count people with no adverse reactions unless they had enrolled in the study, which from the reported adverse reaction rates seems to be a serious problem of the study. This design of the PEI data collection is consistent with the much higher adverse

reaction rate reported in the study, as well as the differences in the ranges of the batch sizes in the two plots presented above, and the fact that the rate of serious adverse reactions were more than twice the rate of all adverse reactions, respectively.

If this was the case, however, this methodology generates a built-in relationship between the number of doses per batch and the number of adverse reactions, thus invariably leading to a highly homogenous linear trend between adverse events and number of doses per batch and with a high degree of determination ($R^2$) exactly as reported by the PEI.

In addition, 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:



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

**ATC CODE: J07BX03[1]**

**AUTHORISATION PROCEDURE in the EU: Centralised**

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**DATE OF THIS REPORT: 19 AUGUST 2021**

**SIGNATURE:** [redacted] **Date**: 19 August 2021

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**Marketing Authorization Holder:**
**BioNTech SE**
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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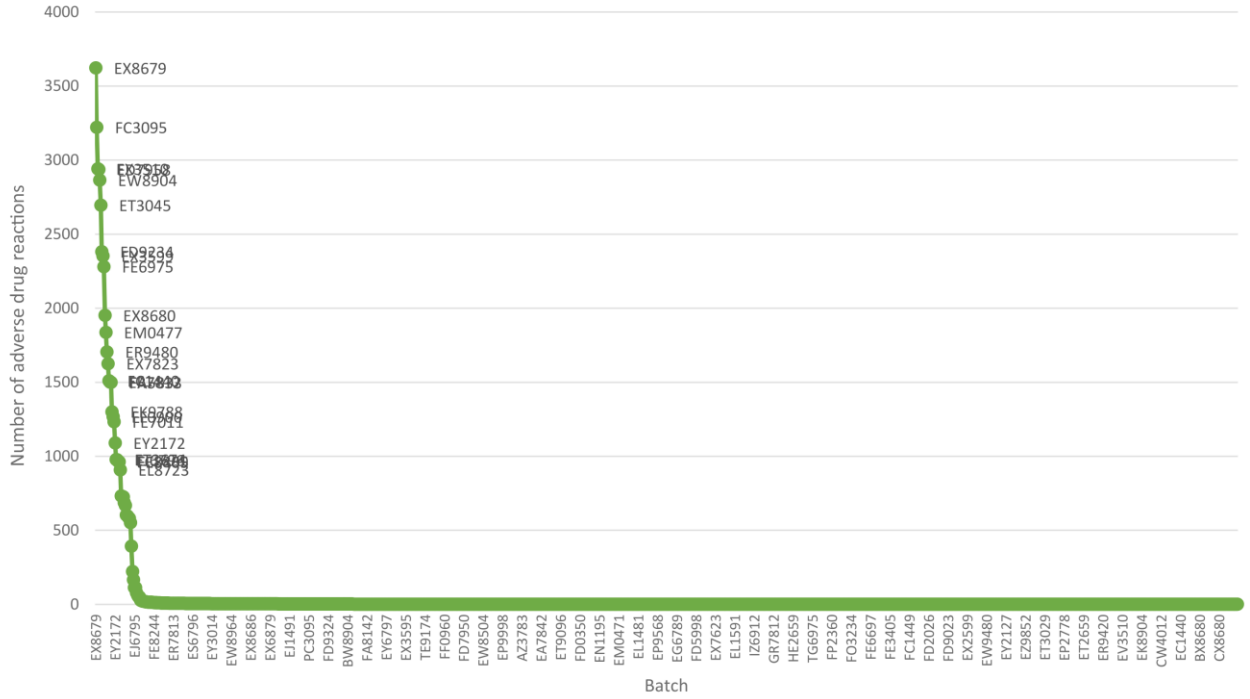
**Table 9. Most Frequently Reported Lot Numbers**

| 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 batches in the blue profile in our Danish study. These data (Table 9, P56-57 in the report) also clearly show a high level of heterogeneity between the number of adverse reactions per batch. Therefore, the current results from PEI are also inconsistent 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. 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, respectively. We eagerly await peer-reviewed academic publication of the PEI results and suggest that in the meantime, the PEI may disclose if the number of registered batch codes in the SafeVac 2.0 database was (erroneously) used for determination of the batch sizes, or, if this was not the case, how the batch sizes were otherwise determined in the study.

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