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RESEARCH LETTER

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Batch-dependent safety of COVID-19 vaccines in the Czech Republic and comparison with data from Denmark

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1 | INTRODUCTION

Recently, a study by Schmeling et al published in your journal raised considerable attention[1] and multiple reactions,[2–4] to which the authors later responded.[5] The authors analysed the number of adverse events (AEs) reported in connection with various batches of COMIRNATY vaccine in Denmark. In almost 11 million doses of 52 different BNT162b2 vaccine batches administered to approximately 4 million Danish individuals, they analysed approx. 43,000 AEs, finding batches with up to .1 reported AEs per dose as well as those with less than .0001 AEs per dose. Interestingly, the high-AE batches were all small (up to 100,000 doses), while the low-AE batches were much larger. Since this important topic has not been further investigated using data from other countries and, therefore, the trends reported by the Danish authors have been neither verified nor refuted, we have decided to follow up on their study using data from the Czech Republic. In our current letter, therefore, we investigated the association of reported AEs after COVID-19 vaccines with the batch numbers in data provided based on a Freedom of Information request filed to the State Institute for Drug Control of the Czech Republic (SUKL) and compared the results to those reported by Schmeling et al. from the Danish registry data.

2 | DATA ACQUIRED

SUKL provided the list of batch numbers for each COVID-19 vaccine type, the date of authorization of the release of each batch, the number of vials in the batch, and the number of AE reports filed to its passive pharmacovigilance system in connection with each of the batches by both healthcare professionals and vaccinated individuals. As all vaccines used in the Czech Republic must be approved by SUKL, the dataset contained all batches of COVID-19 vaccines released for use from the beginning of the vaccination campaign to 1 March, 2023. The data were sent to us on 4 July, 2023. To avoid any confusion, it is necessary to point out that the term 'adverse event' describes a suspected adverse effect, not a proven one.

The data was provided in the form of two XLS files (one for the batch releases and the other for AEs). Each file contained many sheets, basically a single sheet for each vaccine type. Manually copying and pasting the data, we created a single XLS file containing all the information in a machine-readable format (see the data availability section below for all data used in this paper). All the files were provided for public use.

The first batch was released on 23 December, 2020, and the last one on 1 March, 2023. The total number of

[Correction added on 01 July 2024, after first online publication: Second author's name and affiliation 3 were corrected in this version].

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vials released was close to 5.5 million, which translated into almost 35 million doses. Table 1 shows the overview of the data.

3 | AES AND BATCH DIFFERENCES

Based on the data we acquired, a total of 14,386 individual AE reports were filed to the pharmacovigilance system operated by SUKL[6] in association with a COVID-19 vaccine. Note that we have received no direct confirmation that the reports in our particular dataset were deduplicated; however, as SUKL stated in their bulletin[7] that they kept deduplicating all received AE reports, we can reasonably assume that this has been the case in our dataset as well.

A quick summary showed that in the case of COMIRNATY products (combined), there were about 10,700 AE reports in the approx. 28 million doses, which amounts to .38 reports per 1000 doses. For MODERNA products, 1575 AE were reported per 3.8 million doses (.41 reports/1000 doses), and for ASTRAZENECA products, there were 1512 AE reports per 1.1 million doses (1.36 reports/1000 doses). Note that the numbers of doses reported here indicate the numbers of doses released by SUKL, not used doses.

Unfortunately, only 7880 (54%) of AE reports were matched to a particular batch number; in the rest of the reports, the batch number is unknown. Even in the case of deaths, only 99 out of 216 cases (46%) were matched to a particular batch number.

Below, the association between the numbers of AE reports and batch numbers is illustrated in Figure 1. The number of AE reports per 1000 doses is plotted for each batch against the date of the batch release. The 16 different vaccine types listed in Table 1 are colour-coded and the batch size is coded by the dot size.

The top panel of Figure 1 shows the COMIRNATY batches. A large variability in both the size of the batches and the number of AE reports matched to each batch can be observed. For example, batch EJ6796 contained only 9750 doses, yet 54 AE reports were associated with it (5.54 AE reports per 1000 doses). On the other hand, almost no AEs were associated with COMIRNATY Omicron BA 4–5 batches.

The MODERNA products show a similar pattern (the middle panel of Figure 1). The early batches exhibit a large number of AE reports. After June 2021, MODERNA products were coded as SPIKEVAX in the SUKL data, and

Vaccine Type	Number of batches	Number of doses
COMIRNATY	86	19,103,760
COMIRNATY BABY	1	52,800
COMIRNATY DISP	9	2,384,640
COMIRNATY ORIGINAL/OMICRON BA.1	2	1,321,920
COMIRNATY ORIGINAL/OMICRON BA.4–5	14	5,106,240
COMIRNATY ORIGINAL/OMICRON BA.4–5 PED	2	28,800
COMIRNATY PED	10	345,600
COVID-19 VACCINE ASTRAZENECA	11	338,000
COVID-19 VACCINE JANSSEN	18	776,800
COVID-19 VACCINE MODERNA	19	993,800
NUVAXOVID	6	632,000
SPIKEVAX	37	2,415,000
SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.1	7	343,600
SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4–5	3	45,750
VAXZEVRIA	12	775,200
VIDPREVTYN BETA	3	64,800
Total	240	34,728,710

TABLE 1 Overview of the data on all COVID-19 vaccines released by the State Institute for Drug Control of the Czech Republic for distribution in the Czech Republic between December 2020 and March 2023. The 'Vaccine Type' field respects the original data format provided by SUKL, that is, fields corresponding to a single manufacturer were not combined in this table, even if they should designate the same vaccine (e.g. ASTRAZENECA vs. VAXZEVRIA).

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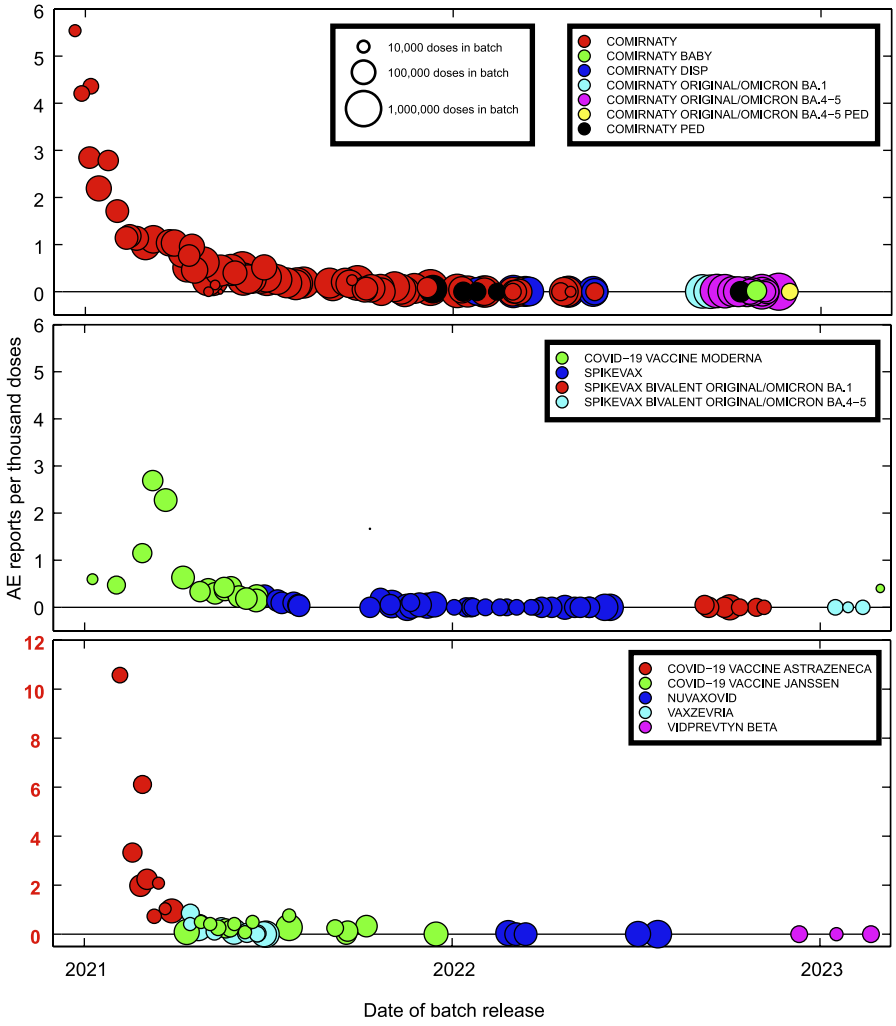

FIGURE 1 The association between the number of adverse event (AE) reports/1000 released doses of each batch and the date of release of the batch. The 16 vaccine types are colour-coded. The dot size shows the size of each batch (on a logarithmic scale—note that these are released doses, not administered doses). Note also the different scales of the y-axis in the bottom panel.

TABLE 2 Reports of adverse events (AEs) for the nine batches of COMIRNATY vaccines present in both our dataset and in the Danish study.[1]

	Czech data			Danish data			
Batch ID	Number of doses	Number of AE reports	AE reports per 1000 doses	Number of doses	Number of AE reports	AE reports per 1000 doses	DK to CZ reporting ratio
EJ6134	19,500	85	4.359	67,860	2193	32.317	7
EJ6790	77,220	88	1.140	56,160	528	9.402	8
EJ6796	9750	54	5.538	11,700	617	52.735	10
EJ6797	144,300	316	2.190	43,290	2002	46.246	21
EK9788	47,775	133	2.784	73,710	1966	26.672	10
ET7205	163,800	170	1.038	2340	7	2.991	3
FD4555	278,460	75	.269	381,420	345	.905	3
FM9088	152,100	6	.039	157,950	0	.000	0
FN5519	625,950	10	.016	193,050	0	.000	0

there was a dramatic decrease in the number of AE reports associated with these later-released batches. Both the bivalent MODERNA products were associated (except for a single batch) with no AE reports at all.

There is a clear indication that the ASTRAZENECA vaccine (bottom panel of Figure 1) was associated with many AE reports at the time of vaccination rollout. For example, the batch ABV2856 contained only 19,200 doses

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but was associated with 203 AE reports. This translates into 10.57 AE reports per 1000 doses. Interestingly, and consistently with the other vaccine types, all batches associated with the highest numbers of AE reports were the ones that were released at the beginning of 2021. Since April 2021, ASTRAZENECA products have been coded as VAXZERVIA in the SUKL data, and they exhibited significantly fewer AE reports. The relatively small sizes of the batches with higher incidences of AE reports observed in our study correspond to the observation by Schmeling et al.[1] that small batches were associated with more AEs. This may be explained by the initial scarcity of supply—the earliest batches might have been divided among many countries in need and, as a result, be smaller in individual countries.

4 | COMPARISON OF THE CZECH AND DANISH PHARMACOVIGILANCE SYSTEMS

The study by Schmeling et al.[1] gave us a unique opportunity to estimate the under-reporting factor in the Czech Republic by comparing the data from the Czech and Danish pharmacovigilance systems. We contacted the authors and asked for the data from their study, which they kindly provided. Nine COMIRNATY batches were present both in their study and in our dataset. Table 2 shows the overview of the number of AE reports associated with these nine common batches. Note that while for the Danish data, we have a confirmation by Schmeling et al. that the data were deduplicated (i.e. multiple reports after a single dose were merged), we have no such definite confirmation for the Czech data, although deduplication is a standard procedure in Czech as well.[7] Still, even if there were differences in processing, the effect of this discrepancy on the outcomes of the comparison is likely to be negligible.

Figure 2 shows a very good correlation (Pearson $c = 0.95$, $p = 0.0004$) between the numbers of AE reports per 1000 doses in Denmark and the Czech Republic for individual batches, proving the validity and good agreement of the reporting patterns in both systems (trends, although not absolute numbers) and, therefore, confirming the results of the study by Schmeling et al.[1] The batch EJ6797 released in December 2020 (one of the first batches released) was associated with the highest number of AE reports in both countries. The lowest numbers of AEs were associated with batches FM9088 and FN5519 that were both released at the beginning of 2022. The slope of the fitted line (see Figure 2) is 9.63 (95% confidence interval 6.79—12.46), which means that the number of AE reports filed in Denmark was, on average, about 10 times higher than in the Czech Republic. We must, however, keep in mind that almost half (46%) of all AE reports in the Czech data have not been paired with the batch (compared to 7% in the Danish data). Assuming an approximately even distribution of such unassigned AEs throughout the batches, we might roughly estimate that 'only' approx. 5.59 times more AE reports per batch were filed in the Danish pharmacovigilance systems compared to the Czech one (54% assigned reports in Czech *9.63 uncorrected CZ/DK underreporting rate /93% assigned reports in Denmark). This implies that even if all AEs were reported in Denmark (which is highly unlikely), the Czech underreporting rate must be at least 82%. Should the underreporting rate in Denmark be in line with the pre-pandemic expectations, that is, somewhere in the region of 95%, this would indicate that less than 1% of AEs were reported in the Czech Republic.

5 | DISCUSSION AND LIMITATIONS

Before the pandemic, it was estimated that globally, a vast majority of AEs were not reported to the pharmacovigilance systems.[8–11] A 2006 systematic review of 27 studies reported that, on average, 6% of AEs were reported.[9] An even higher underreporting rate was found in a recent study on anticoagulants that compared Yellow Card reports to hospital records of gastrointestinal bleeding over

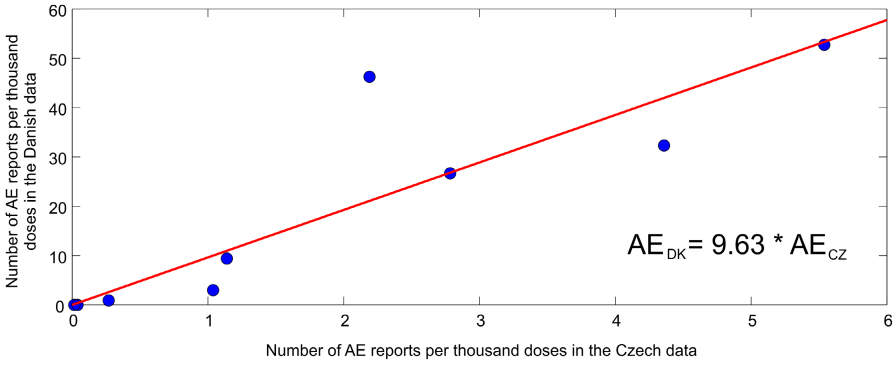

FIGURE 2 The numbers of adverse event (AE) reports per 1000 doses in the Czech (provided by the State Institute for Drug Control of the Czech Republic) and Danish data (kindly provided by Schmeling et al.) using only nine batches that were present in both datasets (all COMIRNATY products).

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5 years.[10] The authors evaluated the underreporting factor in data from a United Kingdom hospital, where more than 12,000 gastrointestinal bleeding-related emergency admissions were recorded. Although approx. 1000 of thus admitted patients were taking direct oral anticoagulants (DOAC), only six DOAC Yellow Card reports were filed by the hospital, representing an approx .5% reporting rate. Similar estimates were provided by Moore and Benett for haemorrhagic and thrombotic complications associated with the uptake of multiple drugs, concluding that only .9%–2.3% of such events were reported.[8] In 2018, the British Medicines and Healthcare Products Regulatory Agency published a call to improve the scheme as it was 'estimated that only 10% of serious reactions and between 2% and 4% of non-serious reactions are reported.'[11] The only data on AE underreporting we have from Denmark concerns angiotensin-converting enzyme inhibitor-related angioedema. In that study, Cornwall et al. concluded that only 1.1% of these AEs were reported in their system.[12] When contemplating whether the more than five-fold difference between the numbers of AE reports in the Czech and Danish pharmacovigilance systems is due to the excellent performance of Danish pharmacovigilance or poor willingness to report AEs in Czechia, the results by Cornwall suggest rather the latter explanation. Unfortunately, such a lack of consistency in reporting at the national level indicates that correct estimation of the frequency of AEs associated with the administration of COVID-19 vaccines may be difficult.

Despite the limitations of our data akin to those voiced by Schmeling et al.[1,5] (such as incomplete or inaccurate data, discussing reports on AEs rather than proven adverse effects) and additional limitations specific to the current report (a large proportion of AEs without a paired batch number, information on doses released to the market rather than administered doses), we have demonstrated a relatively high variability in the number of AE reports associated with various batches of the COVID-19 vaccines of various manufacturers and found similar trends as Schmeling et al. observed for the first year of the use of the COMINARTY vaccine in Denmark. In particular, the batches released early in the vaccination campaign tended to be associated with a high number of AE reports. A logical explanation for this phenomenon might lie in the administration of vaccines at the peak of the pandemic wave and, in effect, some of these AEs might have arisen as a consequence of simultaneous COVID-19 infection rather than of vaccination. However, the almost monotonous character of the graphs in Figure 1 advocates against this hypothesis—had this explanation been valid, the same effect would have to be seen during the first booster campaign that took place at the time of delta and omicron waves (further thoughts on this can be also found in the response paper by Schmeling et al).[5] The fact that almost all doses were utilized in the early stages of the campaign while in the later stages, the majority of vaccines were unused (second and further boosters were used only minimally), offers another possible explanation. However, this hypothesis is disproved by the character of curves in Figure 1: while this explanation could be valid from 2022 onwards, practically all doses of released batches were utilized in the first half of 2021. Still, the number of AE reports declined significantly as early as in the first quarter of 2021.

Changes in the reporting patterns do not seem to fully explain the observed data, either—one would expect the willingness to report AEs to increase over time (especially with the increasing pressure to get vaccinated and, therefore, with vaccination of individuals sceptical of the need of being vaccinated), yet the data show a clear decrease in the number of reports over time. It is, of course, likely that changes in the reporting patterns might have played a role in the later stages but it is highly unlikely that this could cause the steep decline of AE reports over just the first 3 months of the campaign.

Last but not least, the reason for the observed pattern might lie in the suboptimal vaccine manufacturing process at the beginning of the vaccination campaign, which gradually improved over the course of 2021.

In addition, the comparison of Czech and Danish pharmacovigilance data on identical vaccine batches has revealed a superior functioning of the AE reporting system in Denmark compared to the Czech Republic, not only from the perspective of pairing the reported AEs with respective batches but also from the perspective of the underreporting rate. In conclusion, our data from the Czech Republic confirm the batch-dependent safety signal previously observed in relation to COVID-19 vaccines in Denmark. These hypothesis-generating results require further study.

AUTHOR CONTRIBUTIONS

TF – conceptualization, writing of the original draft, statistical analysis, critical revision, final approval. PS – conceptualization, data acquisition, critical revision, final approval. ZK—conceptualization, critical revision, final approval. JJ—conceptualization, writing of the original draft, critical revision, final approval.

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We would like to thank the authors of the original Danish study, especially Max Schmeling, the corresponding author, for their willingness to provide us with the Danish data for comparison.

CONFLICT OF INTEREST STATEMENT

TF, ZK, and JJ are members of the Association of Microbiologists, Immunologists, and Statisticians (Sdruzeni

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mikrobiologu, imunologu a statistiku) in the Czech Republic. They have, however, never received any financial or other incentives that could bias this research and have no financial interests to disclose. Petr Sourek is a journalist.

DATA AVAILABILITY STATEMENT

The original files acquired from SUKL in response to the FOIA request as well as the manually created machine readable file are available at https://github.com/PalackyUniversity/batch-dependent-safety.

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