A Batch-Dependent Safety Signal Related to All-Cause Mortlity Associated with COVID-19 Vaccination

Max Schmeling , Tomáš Fürst , Vibeke Manniche , Peter Riis Hansen , Jonathan D. Gilthorpe *

Posted Date: 6 April 2026

doi: 10.20944/preprints202603.0908.v2

Keywords: COVID-19; vaccine; batch-associated; all-cause mortality; pharmacovigilance; suspected adverse event reports

 doi:10.20944/preprints202603.0908.v2

Article

A Batch-Dependent Safety Signal Related to All-Cause Mortality Associated with COVID-19 Vaccination

Max Schmeling [1], Tomáš Fürst [2], Vibeke Manniche [3], Peter Riis Hansen [4,5] and Jonathan D. Gilthorpe [6,*]

[1] Innometric, Bavnehøjvej 5, Hellum, DK-9520 Skørping, Denmark
[2] Department of Mathematical Analysis and Applications of Mathematics, Faculty of Science, Palacky University Olomouc, 17. listopadu 12, 772 00, Olomouc, Czech Republic
[3] LIVA, Rosenvængets Alle 6A, DK-2100 Copenhagen, Denmark
[4] Department of Cardiology, Copenhagen University Hospital - Herlev and Gentofte, Borgmester Ib Juuls Vej 1, 2730 Herlev, Denmark
[5] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3B, DK-2200 Copenhagen N, Denmark
[6] Department of Medical and Translational Biology, Umeå University, 901 87, Umeå, Sweden
* Correspondence: jonathan.gilthorpe@umu.se

Abstract

Background: Variation in suspected adverse drug reactions (SAR) linked to different batches of COVID-19 vaccines has been reported in several countries, including the Czech Republic, Denmark, Sweden, and the USA. However, SAR data come from spontaneous reporting systems and are subject to under-reporting and other biases. To investigate the potential association between vaccine batches and adverse reactions using an unequivocal endpoint, we examined the temporal relationship between all-cause mortality (ACM) and COVID-19 vaccine type and batch, up to three months after vaccination. **Methods:** We analyzed nationwide data from the Czech Republic on vaccine type and batch, along with corresponding three-month ACM data. Cluster analysis was used to assess age- and sex-specific ACM differences between individual vaccine batches and across vaccine types. We also investigated the relationship between ACM and SAR rates for the same batches. **Results:** During a 21-month period (December 2020 to September 2022), vaccine batches clustered according to their three-month age- and sex-adjusted ACM rates for the four products administered (Comirnaty, Spikevax, Vaxzevria, and Jcovden). For Comirnaty, Spikevax, and Vaxzevria, a clear temporal pattern was observed, with earlier batches showing significantly higher ACM rates. A strong correlation was found between batches that clustered by ACM and those previously identified to cluster by SARs, for all vaccine products except Jcovden. **Conclusions:** Data from the Czech Republic show a clear relationship between administered COVID-19 vaccine batches and 3-month ACM rates for Comirnaty, Spikevax, and Vaxzevria, with earlier batches associated with notably higher ACM. A high correlation between batch-associated ACM and SAR rates for Comirnaty and Spikevax supports the validity of these batch-related safety signals and warrants further investigation using individual-level patient data.

Keywords: COVID-19; vaccine; batch-associated; all-cause mortality; pharmacovigilance; suspected adverse event reports

Introduction

In response to COVID-19, the rapid development and global deployment of vaccines that express the prefusion conformation of the SARS-CoV-2 spike protein in the recipient [1] have been hailed as a pivotal intervention in the pandemic, substantially reducing severe disease and mortality [1,2]. However, these vaccines based on new platforms, such as modified RNA (modRNA) and

 doi:10.20944/preprints202603.0908.v2

adenoviral vector delivery, are associated with an unusually broad spectrum of adverse drug reactions affecting multiple organ systems [3–6]. Furthermore, a single study has suggested increased all-cause mortality (ACM) in young people in the weeks following vaccination [7], albeit this finding was not replicated in self-controlled case series studies [8,9].

Robust and timely pharmacovigilance is essential for safety monitoring of any medical product, especially during a pandemic response. Post-marketing safety surveillance relies on a combination of spontaneous adverse event reporting systems and large-scale epidemiological studies that monitor predefined outcomes [10]. COVID-19 vaccines are unusual in that they are associated with a disproportionately large number of suspected adverse drug reaction (SAR) case safety reports. According to the European Union's pharmacovigilance database EudraVigilance [11], COVID-19 vaccines accounted for 45% of all reports and 23% of all serious reports concerning one or more important medical events over the three-year period from 2021 to 2023 [12]. Spontaneous reporting systems such as EudraVigilance should facilitate the rapid detection of safety signals and are somewhat open to public scrutiny, but are inherently susceptible to under-reporting and other reporting biases, as well as difficulties in establishing causality [13,14].

A relatively underexplored dimension in vaccine safety is the potential for heterogeneity between individual production batches of the same product [15,16]. According to Good Manufacturing Practice, batches must meet stringent quality specifications since subtle variations in components, potency, or purity can affect reactogenicity or safety profiles [17]. Disturbingly, analyses from several countries, including Denmark [18], Sweden [19], the United States [20], and the Czech Republic [21] have reported non-random, batch-associated patterns in SARs for COVID-19 vaccines, suggesting possible batch-dependent heterogeneity. However, whilst raising safety concerns, these findings are constrained by the limitations of SAR data based on voluntary reporting systems.

To investigate this phenomenon using a more robust and definitive endpoint, we turned to ACM, a hard endpoint comprehensively and reliably captured in national registries and less susceptible to ascertainment biases that affect spontaneous reporting. Therefore, this study aimed to determine whether specific batches of COVID-19 vaccines administered in the Czech Republic were associated with heterogeneous short-term ACM rates. Furthermore, we sought to correlate any observed batch-related ACM pattern with previously reported batch-related adverse event patterns to assess the concordance of signals from these orthogonal data sources.

Materials and Methods

Data Sources

Data were obtained on all citizens in the Czech Republic from 1 January 2020 to 13 March 2024 via a freedom of information request (FOIR) to the Institute of Health Information and Statistics (IHIS). Registry data was provided, including a line listing for each individual, with variables for sex, birth year, vaccination date, COVID-19 vaccine product, product manufacturer, batch label code identification (ID), and date of death, if applicable (only available for the period up to and including 31 December 2022). Numbers of SARs per vaccine batch for all COVID-19 vaccine products and numbers of doses per individual batch were obtained for the period up to 13 March 2023 via FOIR to the Czech Republic State Institute for Drug Control (SÚKL). Data for individuals with a missing or incomplete batch ID were excluded. A flow chart of data sources and curation is shown in Figure 1.

 doi:10.20944/preprints202603.0908.v2

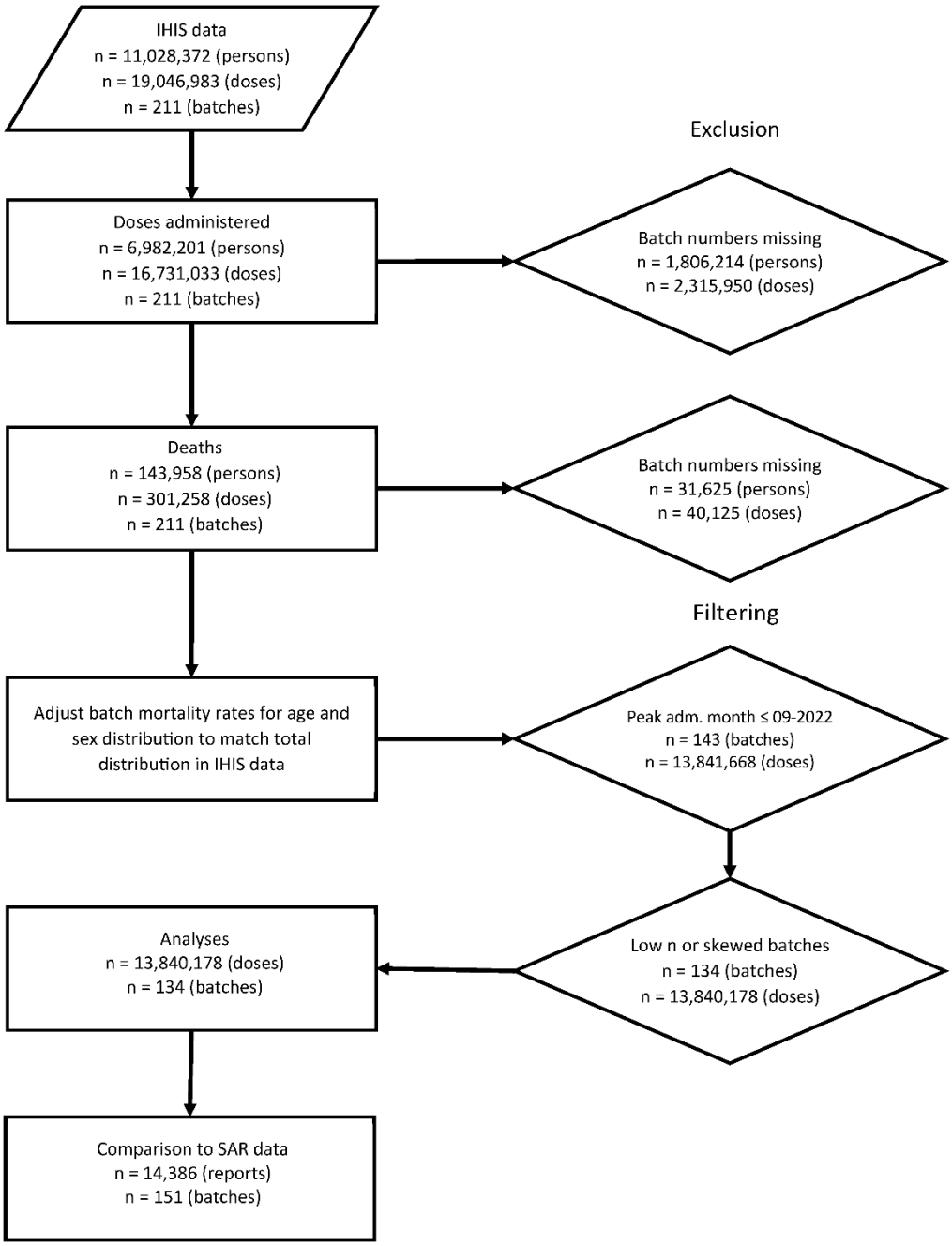

Figure 1. Data sources and curation. Flow chart showing data sources and the number (n) of persons, doses and vaccine batches included or excluded at each processing step as described in Methods. Rhomboid = IHIS data input. Rectangle = data processing step. Diamond = decision step where data was excluded, or subject to filtering, as indicated. IHIS = Institute of Health Information and Statistics of the Czech Republic, SAR = Suspected adverse reaction.

Data Curation

Comirnaty (Pfizer-BioNTech)

In total, 68 batches of Comirnaty were administered during the study. However, batch FR8477 was administered only twice and was omitted from the analysis. Furthermore, batch PCB0017 (1086 administrations), which was administered mainly to younger (mean age 29.4 years) and a few elderly individuals, was associated with 1 death in each of age groups 70-79, 80-89, and 90-99 years, leading to a disproportionally high age-standardized ACM rate and was also excluded from further analysis.

 doi:10.20944/preprints202603.0908.v2

A total of 66 batches remained for analysis with a mean (standard deviation (SD); range) of 170,937 (178,412; 1,245-823,343) doses per batch (Table 1).

Table 1.

Product	Batches (n)	Administered doses per batch (mean (SD))	Administered doses per batch (range)
Comirnaty	66	170,937 (178,412)	1,245-823,343
Spikevax	35	39,483 (26,085)	502-82,070
Vaxzevria	19	42,185 (38,840)	4,968-144,504
Jcovden	14	26,780 (35,242)	9,371-146,120

Spikevax (Moderna)

A total of 40 batches of mRNA-1273 (SPIKEVAX) were administered. Batches 000256A, 016G21A, 000162A, 000202A, and 000384A were only administered 42, 111, 144, 67, and 3 times, respectively, and were not associated with any deaths and were excluded due to their extremely limited utilization. Thus, 35 batches were included for further analysis with a mean (SD; range) of 39,483 (26,085; 502-82,070) doses per batch (Table 1).

Vaxzevria (Astra Zeneca)

A total of 20 batches of ChAdOx1 nCoV-19 (Vaxzevria) were administered. All batches showed a peak of administration between February and July 2021. Batch ABY4055 showed a peak administration in October 2021 and was omitted as only 10 doses were administered and no deaths occurred in these individuals, leaving 19 batches for further analysis with a mean (SD; range) of 42,185 (38,840; 4,968-144,504) doses per batch (Table 1).

Jcovden (Jansen)

In total, 15 batches of Ad26.COV2.S (Jcovden) were administered. Batch ACA4541 was administered only once and was omitted, leaving 14 batches for further analysis with a mean (SD; range) of 26,780 (35,242; 9,371-146,120) doses per batch (Table 1).

Statistical Analyses

The age- and sex-standardized ACM (deaths per 100,000 administered doses) within three months post-vaccination, hereafter termed 'ACM rate', was calculated according to the method specified by the Danish Health Data Authority using direct standardization [9,26]. Deaths and administered doses were aggregated by 10-year age groups and sex, with doses calculated per month. Only batches with maximum monthly usage during the vaccination period (27 December 2020 to 31 September 2022) were selected for further analysis to ensure that mortality data were available for the subsequent three-month follow-up. Accordingly, ACM was calculated for each batch over a three-month window from the date of the last vaccination using available mortality data (1 January 2020 to 31 December 2022). Due to comparison of ACM across non-homogeneous groups, we standardized for sex and age [22–25]. Both crude and standardized ACM rates were calculated for all batches, with administered doses derived directly from registered administrations in the IHIS registry.

To assess heterogeneity in the data, we performed hierarchical cluster analysis (HCA) using between-groups linkage and squared Euclidean distance as a distance measure on 3-month ACM rates to determine the appropriate number of clusters. This was followed by non-hierarchical cluster analysis (N-HCA) to generate final cluster segments. A generalized linear model (GLM) was then used to test for significant separation between clusters.

 doi:10.20944/preprints202603.0908.v2

Statistical significance of deviations in batch-specific ACM rates from the overall mean was assessed using a Z-test, which assumes normality and is appropriate for rates not approaching zero. For rates near zero, testing was performed using the Poisson distribution.

Correlation between ACM rates and SAR rates was assessed using bivariate Pearson correlation with recursive removal of outliers beyond three standard deviations. The number of batches removed per vaccine product was as follows: Comirnaty: 3, Spikevax: 4, Vaxzevria: 0, Jcovden: 0. Since SAR data were not adjusted for age and sex, correlation analyses were performed using crude ACM rates. All analyses were performed in IBM SPSS Statistics (Version 26) [27]. Charts and figures were produced in Microsoft Excel.

Ethical Statement

The study relied solely on anonymized secondary data and was therefore exempt from research ethics board review.

Results

Vaccine Batch ACM Rates: Cluster Analyses

Comirnaty

For Comirnaty, ACM rates (deaths per 100,000 administered doses) varied significantly across batches (mean 260.4, SD 236.7, range 0-1124.4; Supplementary Table S1). Initial HCA identified 3-5 distinct clusters, along with several individual batches that did not cluster. A final N-HCA model with 3 clusters was chosen (Figure 2A), as this was the simplest option which achieved significant separation between clusters using GLM ($p < 0.0001$) and also effectively captured the heterogeneity in the sample. Batches in the blue cluster (n=8) accounted for 4.6% of all doses and were linked to 11.3% of all deaths (R^2 0.99, β 0.00898, 95% confidence interval [CI] 0.00799–0.00996). Batches in the green cluster (n=38) comprised the majority (80.3%) of doses and the majority (79.6%) of deaths (R^2 0.99, β 0.00353, 95% CI 0.00340–0.00367), while batches in the yellow cluster (n=20) accounted for 15.1% of doses and were associated with 9.1% of deaths (R^2 0.98, β 0.00238, 95% CI 0.00222–0.00255).

We previously reported a temporal association between SAR rates and different vaccine batch clusters [19,21,28]. Therefore, we plotted individual batch IDs against their respective ACM rates based on the month of peak administration and observed a temporal pattern where ACM rates and clustered batches aligned, though without an obvious seasonal trend(Figure 2B). However, batches in the blue cluster were administered early in the vaccination campaign, followed by most batches in the green cluster, and later on by batches in the yellow cluster, with some overlap between the green and yellow clusters during the later study period. Additionally, all batches except one in the blue cluster showed a significant positive deviation from the overall mean ACM rate of 954.3 (SD 101.1; $p \leq 0.0364$; Table S1). Notably, several batches in the yellow cluster showed a significant negative deviation from the mean mortality rate, including EX8680 (0.0; $p < 0.001$; Table S1), FN4071, FN4072, and FN6988 (0.1462 $p < 0.001$; Table S1).

Spikevax

For Spikevax, the ACM rate also varied considerably (mean 419.9, SD 402.3, range 0-2385.1; Table S1). Initial HCA identified one large cluster (33 batches) and one small cluster (2 batches). Non-N-HCA resulted in four clusters, but two of these clusters each contained a single batch, which were then combined into one cluster (Figure 2C, blue cluster) containing 2 batches for optimal separation. The remaining batches were distributed between two additional clusters with 22 (green cluster) and 11 (yellow cluster) batches, respectively The separations between the three resulting clusters (Figure 2C) were highly significant when tested by use of GLM ($p \leq 0.0001$ for all). Batches in the blue cluster (n=2) accounted for 2.0% of all doses and were associated with 7.5% of all deaths in the 3-month period after vaccination (R^2 0.97, β 0.01406 (95% CI -0.01361–0.04173). Batches in the green cluster

 doi:10.20944/preprints202603.0908.v2

(n=18) comprised 70.7% of doses and 74.7% of deaths (R^2 0.98, β 0.00431, 95% CI 0.00401–0.00462), while batches in the yellow cluster (n=15) represented 27.4% of doses and were linked to 17.8% of deaths (R^2 0.99, β 0.00271, 95% CI 0.00256–0.00286).

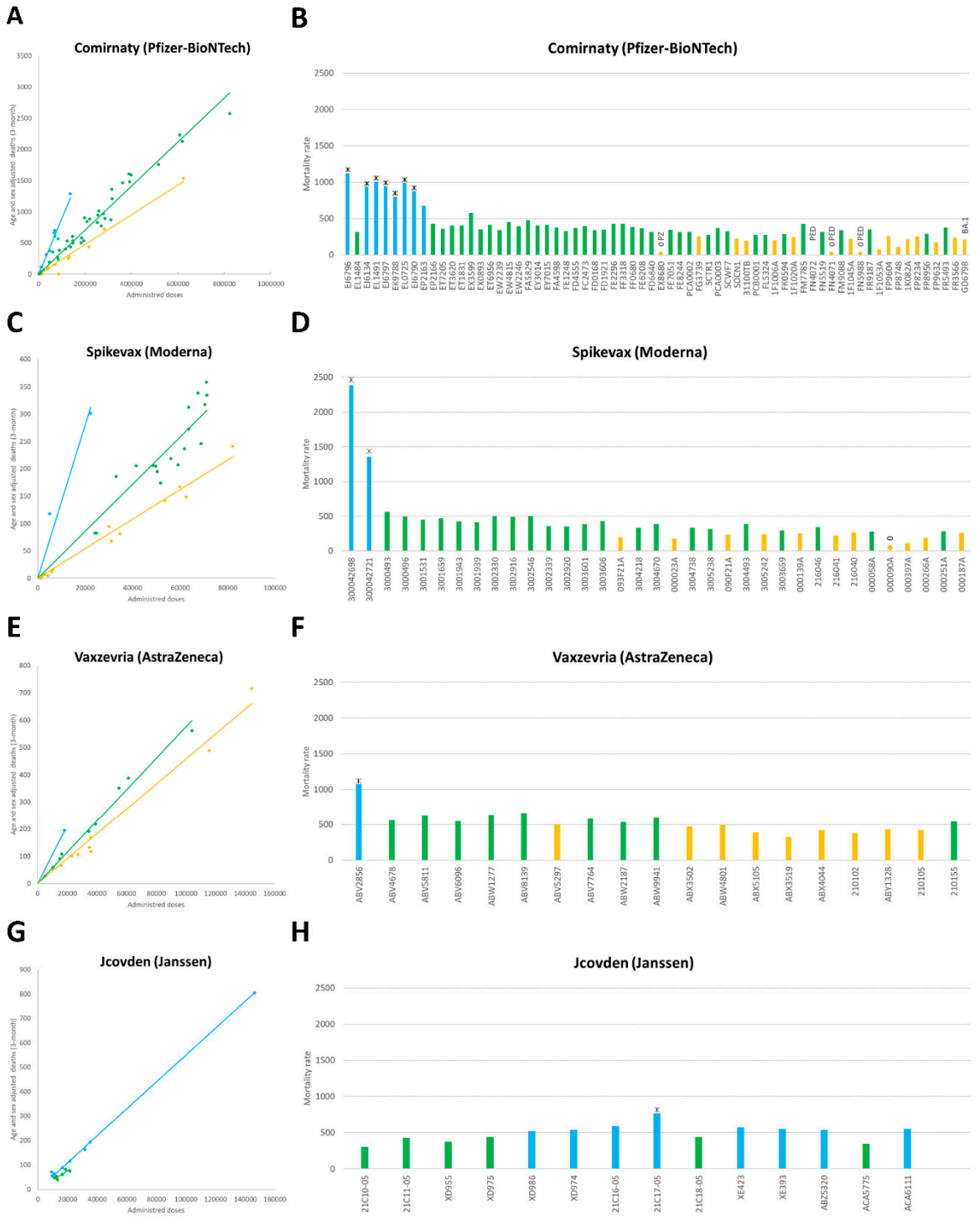

Figure 2. Cluster analysis of batch-related age- and sex adjusted three-month all-cause mortality. A, C, E, and G: Scatter plots showing vaccine batches plotted by the number of administered doses (x-axis) versus the number of age- and sex-adjusted deaths (y-axis). Each point represents a single vaccine batch. Trendlines are linear regression lines. **A** (Comirnaty); Blue: R^2 0.99, β 0.00898, 95% confidence interval [CI] 0.00799–0.00996. Green: R^2 0.99, β 0.00353, 95% CI 0.00340–0.00367. Yellow: R^2 0.98, β 0.00238, 95% CI 0.00222–0.00255. **C** (Spikevax); Blue: R^2 0.97, β 0.01406, 95% CI -0.01361–0.04173. Green: R^2 0.98, β 0.00431, 95% CI 0.00401–0.00462. Yellow: R^2 0.99, β 0.00271, 95% CI 0.00256–0.00286. **E** (Vaxzevria); Blue: R^2 1, β 0.01072 (95% CI not applicable). Green: R^2 0.99,

 doi:10.20944/preprints202603.0908.v2

β 0.00575, 95% CI 0.00340–0.00613. Yellow: R^2 0.99, β 0.00457, 95% CI 0.00420–0.00495. **G** (Jcovden); Blue: R^2 0.999, β 0.0055, 95% CI -0.00537–0.00564. Green: R^2 0.985, β 0.00383, 95% CI 0.00330–0.00437. **B, D, F, and H**: Column charts displaying the sex-standardized all cause mortality rates (deaths per 100,000 administered doses for each vaccine batch by the month of peak administration), matched with the corresponding color coding for clusters in panels **A, C, E, and G**, respectively.

As observed with Comirnaty, Spikevax batches that clustered together also exhibited a temporal pattern, with a clear separation between batches in the blue and green clusters and some overlap between batches in the green and yellow clusters (Figure 2D). A significant positive deviation from the overall mean ACM rate was found for the two batches in the blue cluster (mean 1971.6, SD 726.3, $p \leq 0.0099$; Table S1), followed by a decrease in ACM rates over time for subsequent batches.

Vaxzevria

For Vaxzevria, the ACM rate varied significantly (mean 538.1, SD 161.3, range 324.6-1072.2; Table S1). HCA produced either 2 or 3 clusters, whereas subsequent non-HCA yielded 3 clusters, each with significant separation (GLM; $p < 0.0001$). Similar to Comirnaty and Spikevax, Vaxzevria ACM rates also showed a comparable temporal pattern with vaccine batches, with batches separated in the blue (n=1) and green (n=9) clusters, and overlap between the green and yellow (n=9) clusters (Figure 2E). A significant positive deviation from the mean overall ACM rate was observed for the single batch in the blue cluster (batch ID ABV2856; mean 1072.2, $p < 0.0023$; Table S1).

Batches in the blue cluster (n=1) accounted for 2.3% of all doses and were associated with 4.7% of all deaths (R^2 1, β 0.01072, 95% CI not applicable). Batches in the green cluster (n=9) made up approximately half of the doses 42.5% and related deaths 48.3% (R^2 0.99, β = 0.00575, 95% CI 0.00340–0.00613), while batches within the yellow cluster (n=9) represented 55.3% of doses and were linked to 47.0% of deaths (R^2 0.99, β 0.00457, 95% CI 0.00420–0.00494).

JCovden

For Jcovden, the ACM rate also varied significantly (mean 496.0, SD 118.0; range 304.4-756.3; Table S1). HCA resulted in 2-3 clusters, and non-HCA yielded 2 clusters with significant separation ($p \leq 0.0001$). In contrast to Comirnaty, Spikevax, and Vaxzevria, Jcovden batches in the same cluster did not show a clear temporal relationship with ACM rates (Figure 2F). A single batch from the blue cluster (batch ID 21C17-05) showed a significant positive deviation from the mean ACM rate (mean 765.3, $p \leq 0.0113$).

Batches in the blue cluster (n=8) accounted for 75.0% of all doses and were associated with 81.2% of all deaths (R^2 0.999, β 0.0055, 95% CI -0.00537–0.00564). Batches in the green cluster (n=6) comprised 25.0% of doses and 18.8% of related deaths (R^2 0.985, β 0.00383, 95% CI 0.003295–0.004373). No temporal relationship was observed between ACM rates and the batch clusters.

Relationship Between ACM and SARs

To examine the relationship between ACM and SAR rates, we utilized previously published data from the Czech Republic [21] to calculate crude SAR rates (since available data did not allow for age and sex adjustment) and compared these with the crude ACM rates for the corresponding batches (Table S1). After removing outliers (EL1484, EJ6796, and EX8680 for Comirnaty and 300493, 300496, and 3001531 for Spikevax; Fig. 3A and B, respectively), which deviated substantially, a strong correlation was observed between ACM and SAR rates for Comirnaty (R 0.82; Figure 3A), Spikevax (R 0.69; Figure 3B), and Vaxzevria (R 0.82; Figure 3C), while a notable correlation was not observed for Jcovden (R 0.27; Figure 3D). Comparable results were observed in a sensitivity analysis using age- and sex-adjusted ACM rates (not shown).

 doi:10.20944/preprints202603.0908.v2

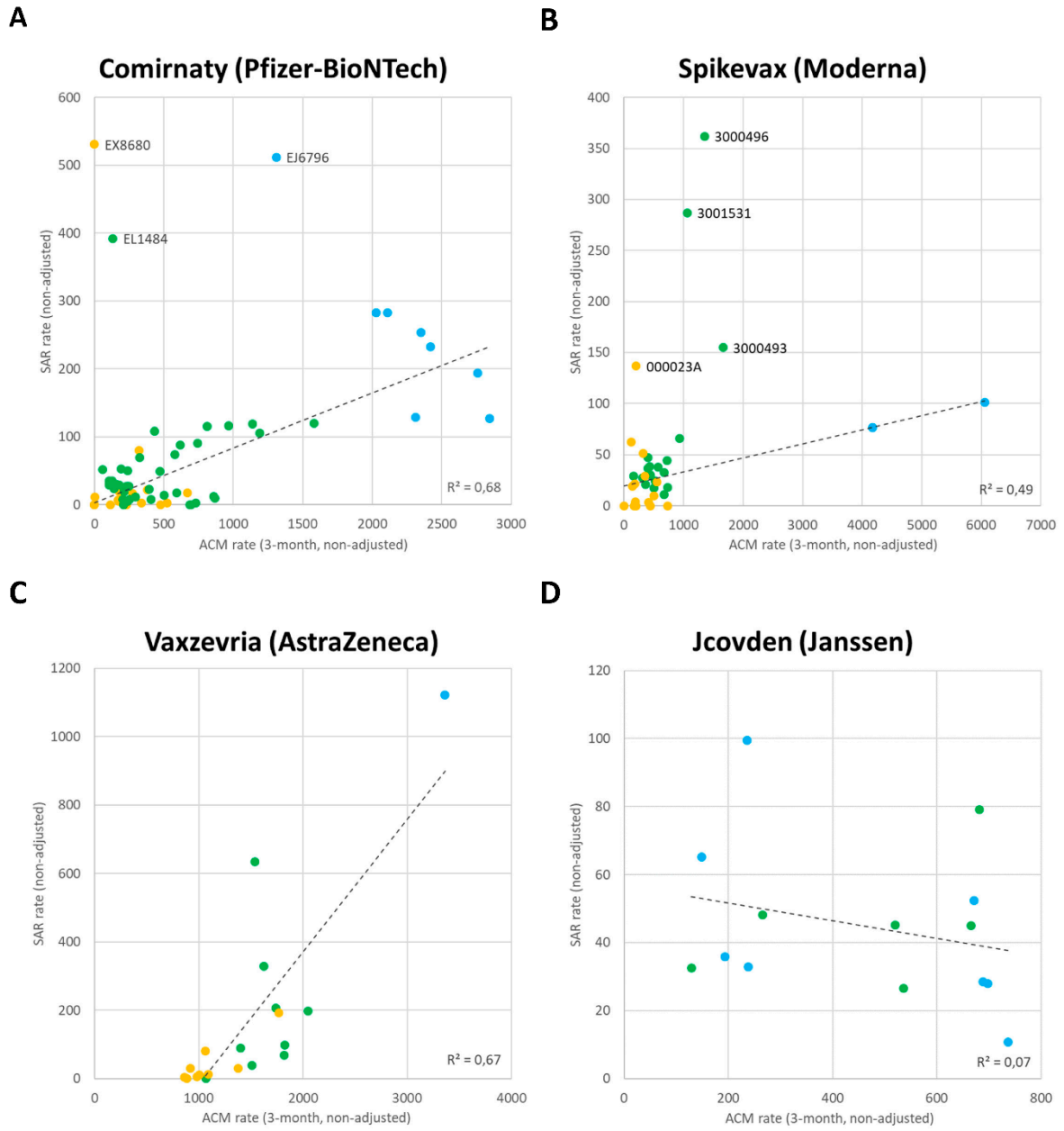

Figure 3. Correlation between batch-related 3-month all-cause mortality (ACM) and suspected adverse reactions (SARs). Scatter plots showing the relationship between 3-month ACM and SAR report data for (**A**) Comirnaty, (**B**) Spikevax, (**C**) Vaxzevria, and (**D**) Jcovden. Each point represents a single vaccine batch color-coded as in Figure 2. Dashed trendlines are linear regression lines. The coefficient of determination (R^2) is shown in the bottom right of each plot.

Discussion

In the current nationwide study of the Czech Republic, we identified COVID-19 vaccine batches with significantly higher or lower age- and sex-adjusted ACM rates than other batches of the same product. This relationship demonstrated a clear temporal trend and, for three of the four products studied (Comirnaty, Spikevax, and Vaxzevria), but not for Jcovden, notably higher ACM rates were associated with batches administered early in the vaccination campaign. Similarly, strong correlations with SAR rates were found for these three products.

Remarkable platform-dependent differences in the safety profiles of COVID-19 vaccines have been reported [29]. Whilst our findings do not establish causality at the individual level between COVID-19 vaccine administration and ACM, they highlight important questions for the safety

 doi:10.20944/preprints202603.0908.v2

monitoring of COVID-19 vaccines, especially those using the modRNA platform. Indeed, the strong correlation between batch-associated ACM and SAR, which has not been explored for COVID-19 vaccines, supports a genuine safety signal rather than residual confounding. It is notable that ACM and SAR data are largely independent. SAR reports come from a spontaneous reporting system, which is susceptible to under-reporting and other biases, while ACM is a definitive endpoint from reliable national mortality records. Accordingly, the convergence of signals from these separate sources greatly strengthens the evidence for the existence of a non-random phenomenon.

The results of this study support earlier preliminary reports of batch-dependent SAR patterns in the Czech Republic [21], Denmark [19,28], Sweden [19], and the United States [20]. They differ from subsequent findings of Hviid *et al.*, who reported no meaningful difference in 28-day ACM and hospitalisations for potential adverse events for Danish vaccine batches [31]. However, methodological limitations of that study may have diluted a potential ACM-associated signal, and the uncertain relationship between SARs, short-term hospitalizations, and long-term prognostic consequences preclude definitive conclusions [30]. Moreover, population-based self-controlled case series have suggested that ACM was not significantly increased up to 3 months after COVID-19 vaccination (Nafilyan et al. 2023, Xu et al. 2024). However, these studies did not examine the potential batch-dependency of ACM and it is possible, for example, that in such summary data, signals from batches with increased ACM rates were significantly diluted by those with lesser ACM rates.

Our data confirmed not only a temporal decline in batch-associated ACM but also a correlation between ACM and SAR rates within the Czech population. Indeed, the strong correlations between ACM and SAR rates observed, not least for the two modRNA vaccine batches, reinforce the possibility of significant batch-to-batch product differences. Potential contributory causal factors may include modRNA integrity [32,33], Spike protein expression dynamics [34,35], residual DNA [36] or endotoxin [37] and the reformulation of the buffer component (from PBS to Tris) of the Comirnaty drug product [38].

The main strength of this study is the analysis of a comprehensive population-level ACM dataset that complements accompanying SAR data. Key limitations must be acknowledged. First, although we adjusted for age and sex, population-level data cannot account for all individual-level confounders, such as specific comorbidities and may not fully account for all underlying health vulnerabilities (and temporal shifts herein) in the vaccinated population. Second, we only assessed ACM rates within a three-month period after vaccination and potential batch-dependent effects on longer-term ACM remain to be determined. Lastly, while ACM exhibits seasonal trends, we did not observe a pattern linking batch-related ACM to seasonality, indicating that it was not a primary factor in our results. It is also important to highlight that potential COVID-19 vaccine-induced mortality is likely only a small part of total ACM. However, in view of global COVID-19 vaccination implementation, even minor, systematic differences in ACM rates across batches deserve careful examination as possible safety signals.

Conclusion

COVID-19 vaccine batches administered in the Czech Republic were associated with significantly different rates of age- and sex-adjusted 3-month ACM rates. For Comirnaty, Spikevax, and Vaxzevria, batches administered earlier were linked to higher ACM rates. The correlation also observed between ACM and SAR rates for these batches strengthens the evidence for a batch-dependent safety signal. These results warrant further investigation through detailed medical record reviews, analysis of pathological specimens where available, and quality-control re-evaluation of retained COVID-19 batch samples.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Supplementary Table S1: Summary of vaccine batch data.

Author Contributions: Conceptualization: MS, TF, VM; Methodology: MS, TF; Investigation: All authors; Data curation: MS, TF; Formal analysis: MS, TF, VM, PRH, JDG; Writing original draft: MS, JDG; Review and editing:

 doi:10.20944/preprints202603.0908.v2

All authors; Project administration: VM; Funding acquisition: VM. All authors reviewed and agreed upon the final version of the manuscript.

Funding: This study was funded by donation-based crowdfunding (Danish Ministry of Justice, Department of Civil Affairs, 23-700-06725). The funding source did not influence the design or completion of the study, the writing of the manuscript, or the decision to submit it for publication.

Data Availability Statement: The original data used in the study are publicly available at https://github.com/Schmeling-M/C-19-ACM-CZ-data.

Conflicts of interest: None.

References

1. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
2. Semenzato L, Le Vu S, Botton J, Bertrand M, Jabagi MJ, Drouin J, et al. COVID-19 mRNA Vaccination and 4-Year All-Cause Mortality Among Adults Aged 18 to 59 Years in France. JAMA Netw Open. 2025;8(12):e2546822.
3. Guo W, Deguise J, Tian Y, Huang PC, Goru R, Yang Q, et al. Profiling COVID-19 Vaccine Adverse Events by Statistical and Ontological Analysis of VAERS Case Reports. Front Pharmacol. 2022;13:870599.
4. Szebeni J. Expanded Spectrum and Increased Incidence of Adverse Events Linked to COVID-19 Genetic Vaccines: New Concepts on Prophylactic Immuno-Gene Therapy, Iatrogenic Orphan Disease, and Platform-Inherent Challenges. Pharmaceutics. 2025;17(4).
5. Bartmann C, Schmidt V, Morz M, Schwab M, Rehn M, Blau-Schneider B, et al. Detection of spike protein in term placentas of COVID-19 vaccinated and/or SARS-CoV-2 infected women. PLoS One. 2026;21(3):e0344185.
6. Kuperwasser C, El-Deiry WS. COVID vaccination and post-infection cancer signals: Evaluating patterns and potential biological mechanisms. Oncotarget. 2026;17:1-29.
7. Aarstad J. Deaths among young people in England increased significantly in 10 of 11 weeks after COVID-19 vaccination and doubled in three. EXCLI J. 2024;23:908-11.
8. Nafilyan V, Bermingham CR, Ward IL, Morgan J, Zaccardi F, Khunti K, et al. Risk of death following COVID-19 vaccination or positive SARS-CoV-2 test in young people in England. Nat Commun. 2023;14(1):1541.
9. Xu S, Sy LS, Hong V, Farrington P, Glenn SC, Ryan DS, et al. Mortality risk after COVID-19 vaccination: A self-controlled case series study. Vaccine. 2024;42(7):1731-7.
10. Imbrici P, De Bellis M, Liantonio A, De Luca A. Investigating the Benefit-Risk Profile of Drugs: From Spontaneous Reporting Systems to Real-World Data for Pharmacovigilance. Methods Mol Biol. 2025;2834:333-49.
11. Postigo R, Brosch S, Slattery J, van Haren A, Dogne JM, Kurz X, et al. EudraVigilance Medicines Safety Database: Publicly Accessible Data for Research and Public Health Protection. Drug Saf. 2018;41(7):665-75.
12. European Medicines Agency. EudraVigilance - European database of suspected adverse drug reaction reports [cited 2026 10/03/2026]. Available from: https://www.adrreports.eu/en/.
13. Dubrall D, Christ P, Domgorgen S, Schmid M, Sachs B. Factors associated with the completeness of information provided in adverse drug reaction reports of physicians, pharmacists and consumers from Germany. Sci Rep. 2025;15(1):23751.
14. Leitzen S, Dubrall D, Toni I, Stingl J, Christ P, Koberle U, et al. Adverse Drug Reactions in Children: Comparison of Reports Collected in a Pharmacovigilance Project Versus Spontaneously Collected ADR Reports. Paediatr Drugs. 2023;25(2):203-15.
15. De Mattia F, Chapsal JM, Descamps J, Halder M, Jarrett N, Kross I, et al. The consistency approach for quality control of vaccines - a strategy to improve quality control and implement 3Rs. Biologicals. 2011;39(1):59-65.

 doi:10.20944/preprints202603.0908.v2

16. European Medicines Agency. ICH: Q 5 E: Comparability of biotechnological/biological products - Step 5. NOTE FOR GUIDANCE ON BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS (CPMP/ICH/5721/03)2005; CPMP/ICH/5721/03.
17. Bruce Yu Y, Taraban MB, Briggs KT. All vials are not the same: Potential role of vaccine quality in vaccine adverse reactions. Vaccine. 2021;39(45):6565-9.
18. Schmeling M, Manniche V, Hansen PR. Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine. Eur J Clin Invest. 2023;53(8):e13998.
19. Manniche V, Schmeling M, Gilthorpe JD, Hansen PR. Reports of Batch-Dependent Suspected Adverse Events of the BNT162b2 mRNA COVID-19 Vaccine: Comparison of Results from Denmark and Sweden. Medicina (Kaunas). 2024;60(8).
20. Jablonowski K HB. Batch-dependent Safety of the BNT162b2 mRNA COVID-19 Vaccine in the United States. . Science, Public Health Policy and the Law 2024;v5.2019-2024(2024 Sep 26; v5.2019-2024).
21. Furst T, Sourek P, Kratka Z, Janosek J. Batch-dependent safety of COVID-19 vaccines in the Czech Republic and comparison with data from Denmark. Eur J Clin Invest. 2024;54(10):e14271.
22. Forthun I, Madsen C, Emilsson L, Nilsson A, Kepp KP, Bjork J, et al. Excess mortality in Denmark, Finland, Norway and Sweden during the COVID-19 pandemic 2020-2022. Eur J Public Health. 2024;34(4):737-43.
23. Hong D, Lee S, Choi YJ, Moon S, Jang Y, Cho YM, et al. The age-standardized incidence, mortality, and case fatality rates of COVID-19 in 79 countries: a cross-sectional comparison and their correlations with associated factors. Epidemiol Health. 2021;43:e2021061.
24. Kepp KP, Bjork J, Emilsson L, Lallukka T. The contribution of population age-sex structure to the excess mortality estimates of 2020-2021 in Denmark, Finland, Iceland, Norway, and Sweden. SSM Popul Health. 2023;22:101377.
25. Eurostat. Revision of the European Standard Population: Report of Eurostat's task force. ISBN 978-92-79-31094-2 ed2013.
26. Sundhedstyrelsen. Analysevariable og statistiske mål for statistikken om kroniske sygdomme og svære psykiske lidelser 2026 [Available from: https://cdn1.gopublic.dk/sundhedsdatastyrelsen/Media/638941202128671349/RUKS%20analysevariable%20og%20statistiske%20m%C3%A5l.pdf
27. IBM SPSS Statistics for Windows. Version 26.0 ed2020.
28. Schmeling M, Manniche V, Hansen PR. Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine. Eur J Clin Invest. 2023;53(12):e14102.
29. Choi MJ, Na Y, Hyun HJ, Nham E, Yoon JG, Seong H, et al. Comparative safety analysis of mRNA and adenoviral vector COVID-19 vaccines: a nationwide cohort study using an emulated target trial approach. Clin Microbiol Infect. 2024;30(5):646-52.
30. Schmeling M, Manniche V, Hansen PR. Safety of BNT162b2 mRNA COVID-19 Vaccine Batches: A Nationwide Cohort Study. Pharmacoepidemiol Drug Saf. 2025;34(11):e70270.
31. Hviid A, Svalgaard IB. Safety of BNT162b2 mRNA COVID-19 Vaccine Batches: A Nationwide Cohort Study. Pharmacoepidemiol Drug Saf. 2025;34(9):e70207.
32. Tinari S. The EMA covid-19 data leak, and what it tells us about mRNA instability. BMJ. 2021;372:n627.
33. European Medicines Agency. European public assessment report (EPAR) 2020 2020 [Available from: https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf.
34. Azzarone B, Landolina N, Mariotti FR, Moretta L, Maggi E. Soluble SARS-CoV-2 Spike glycoprotein: considering some potential pathogenic effects. Front Immunol. 2025;16:1616106.
35. Brogna C, Cristoni S, Marino G, Montano L, Viduto V, Fabrowski M, et al. Detection of recombinant Spike protein in the blood of individuals vaccinated against SARS-CoV-2: Possible molecular mechanisms. Proteomics Clin Appl. 2023;17(6):e2300048.
36. Speicher DJ, Rose J, McKernan K. Quantification of residual plasmid DNA and SV40 promoter-enhancer sequences in Pfizer/BioNTech and Moderna modRNA COVID-19 vaccines from Ontario, Canada. Autoimmunity. 2025;58(1):2551517.

 doi:10.20944/preprints202603.0908.v2

37. Yamaguchi T, Ogawa T, Ando T, Yoshida S, Sakurai A, Maki K, et al. Points-to-consider: the mRNA vaccine reflection paper. Translational and Regulatory Sciences. 2024;6(1):20–7.
38. FDA Briefing Document - Vaccines and Related Biological Products Advisory Committee Meeting October 26, 2021 2021 [Available from: https://www.fda.gov/media/153447/download.