Brief Report

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Batch-Dependent Safety Signal: Nationwide Analysis of Suspected Adverse Events Following COVID-19 Vaccination in Germany

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Abstract

Background: Preliminary reports have suggested a batch-dependent safety signal for COVID-19 vaccines. It is important to establish if these findings can be replicated. **Methods:** We used publicly available nationwide data from Germany spanning the first 3.5 years of the vaccination campaign to calculate weekly rates of spontaneously reported suspected adverse events (SAEs) per 1 000 administered vaccine doses. **Results:** SAE rates ranged between 2.2 and 22.8 per 1 000 doses and women accounted for 72% of all SAEs. Crucially, SAE rates for Comirnaty (Pfizer-BioNTech), Spikevax (Moderna), and Vaxzevria (AstraZeneca) were very high in the initial phase of vaccination rollout and hereafter declined precipitously. For example, SAE rates in weeks 1-4 of 2021 were 8.2, 50.8, and 620.9 per 1 000 doses of Comirnaty, Spikevax, and Vaxzevria, respectively, but fell to 4.4, 11.6, and 7.4 per 1 000 doses in weeks 12-16 of 2021. **Conclusions:** SAE rates in Germany were highly elevated in the initial phase of COVID-19 vaccination rollout and then fell precipitously, a pattern compatible with a batch-dependent safety signal. Furthermore, there was a considerable overrepresentation of women with SAEs. These preliminary results call for more definitive studies of batch-dependent COVID-19 vaccine safety.

Keywords: COVID-19; vaccine; adverse effects; vaccine safety; pharmacovigilance

Introduction

In the wake of the swift and unprecedented industrial upscaling of global COVID-19 vaccine production, preliminary reports from Denmark, Sweden, the Czech Republic, and the US have described vaccine batch-dependent differences in rates of reported suspected adverse events (SAEs).[1–4] These reports primarily concerned the BNT162b2 modified mRNA vaccine (Comirnaty [Pfizer-BioNTech]) and showed very high SAE rates during the initial vaccination rollout.[1–4] The results generated considerable controversy by questioning COVID-19 vaccine quality control and regulatory oversight of SAEs at vaccine batch level.[5–7] For other pharmaceutical products, an emergent batch-dependent safety signal would likely have triggered immediate precautionary

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regulatory action and prompted definitive follow-up studies. However, to date only a single subsequent study of the batch-dependent safety of the BNT162b2 vaccine has been published.[8] Given this evidence gap, more replication studies are clearly warranted and we therefore examined SAE rates after COVID-19 vaccination in Germany.

Material and Methods

Data on individual case identifiers of spontaneously reported SAEs of COVID-19 vaccines in the period from 27 December 2020 to 30 June 2024 in Germany, including sex, age categories (<18 years, 18-59 years, and ≥60 years), vaccination dates, vaccine types, vaccine batch numbers, and dates of SAE onset, respectively, were retrieved from the publicly accessible homepage of the Paul Erlich Institute in Langen, Germany, which is responsible for authorization and monitoring of the quality, efficacy and safety of medicinal products including vaccines in Germany.[9] Data on the number of administered COVID-19 vaccines doses in Germany in the period from 27 December 2020 to 4 July 2024, the federal states where respective vaccinations took place, dose sequence number (first, second, etc.), and numbers of individuals vaccinated on each day the with the respective vaccine types, were retrieved from the homepage of the Robert Koch Institute in Berlin.[10] By combining these data, the total numbers of administered vaccine doses, total numbers of reported SAEs, and SAEs per 1 000 doses for each vaccine type were determined. Weekly (ISO week calendar) numbers of reported SAEs per 1 000 doses were calculated for each COVID-19 vaccine type by dividing the accumulated number of SAEs per week, with the number of doses of this vaccine type which were administered that week. In addition, we assessed the mean time in days between vaccination and SAE onset. The study used publicly available anonymized data and was therefore exempt from ethics review.

Results

A total of 197 033 869 COVID-19 vaccine doses were administered in Germany during the study period with rates of SAEs ranging between 2.2 and 22.8 SAEs per 1 000 doses across vaccine types (Table 1). In 2021, 2022, 2023, and the first half of 2024, total numbers of SAEs were 601 610, 317 453, 55 755, and 26 608, respectively. Each year, most SAEs occurred in women, and throughout the entire study period, women accounted for about 72% of all SAEs. The age distribution of subjects with SAEs somewhat varied over time. For example, for SAEs with reported onset in weeks 1-4 of 2021, approximately 6%, 76%, and 18 % of SAEs were experienced by subjects <18, 18-59, and ≥60 years of age, respectively, while for SAEs with onset in weeks 12-16 of 2021, 3%, 64%, and 33% of subjects were <18, 18–59, and ≥60 years of age, respectively. Overall, about 56% of SAEs occurred within 0–1 day, 82% within 14 days, and 18% more than 14 days after vaccination, a pattern consistent across all vaccine types.

Table 1. Summary of COVID-19 vaccine types, administered doses, and reported suspected adverse events (SAEs) per 1 000 doses.

COVID-19 vaccine type	Total doses (n)	SAEs (n)	SAEs per 1 000 doses
Comirnaty (Pfizer-BioNTech)[1]	148 488 694	582 197	3.9
Spikevax (Moderna)[1]	31 801 678	187 912	5.9
Vaxzevria (AstraZeneca)[2]	12 805 337	185 360	14.5
Jcovden (Janssen)[2]	3 768 545	36 304	9.6
Nuvaxovid (Novavax)[3]	161 076	3 676	22.8
Valneva (Valneva SE; Dynavax)[4]	8 151	18	2.2
VidPrevtyn Beta (Sanofi-Pasteur, GSK)[5]	415	0	0.0
Unknown	0	5 958	
Total	197 033 869	1 001 426	

[1]Modified mRNA vaccine, [2]Adenoviral vector vaccine, [3]Recombinant nanoparticle vaccine, [4]Whole inactivated virus vaccine, [5]Recombinant protein subunit vaccine.

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A striking temporal pattern in weekly SAE rates was observed for the three predominant vaccines Comirnaty (Pfizer-BioNtech), Spikevax (Moderna), and Vaxzevria (AstraZeneca). As shown in Figure 1, SAE rates were exceptionally high immediately after introduction of the vaccines, before falling precipitously during the first quarter of 2021 and remaining low hereafter. Indeed, between weeks 1-4 and 12-16 of 2021, mean SAEs per 1 000 administered doses fell from 8.2 to 4.4 (Comirnaty), 11.6 to 7.4 (Spikevax), and 620.9 to 7.4 (Vaxzevria), respectively. At the batch level, the high SAE rates in the initial period (weeks 1-4 of 2021) were associated with a limited number of distinct vaccine batch numbers (n=61, 48, and 9, respectively). As the sharp decline in SAE levelled off (weeks 12-16 of 2021), SAE reports were distributed across more batches (n=99, 35, and 35, respectively), and the average number of administered doses per batch increased from 17 695 to 83 199. Vaccines introduced later (Jcovden [Janssen], Nuvaxovid [Novavax], and VidPrevtyn Beta [Sanofi-Pasteur, GSK]) were used much less intensively but also exhibited a similar pattern of higher initial SAE rates early after rollout.

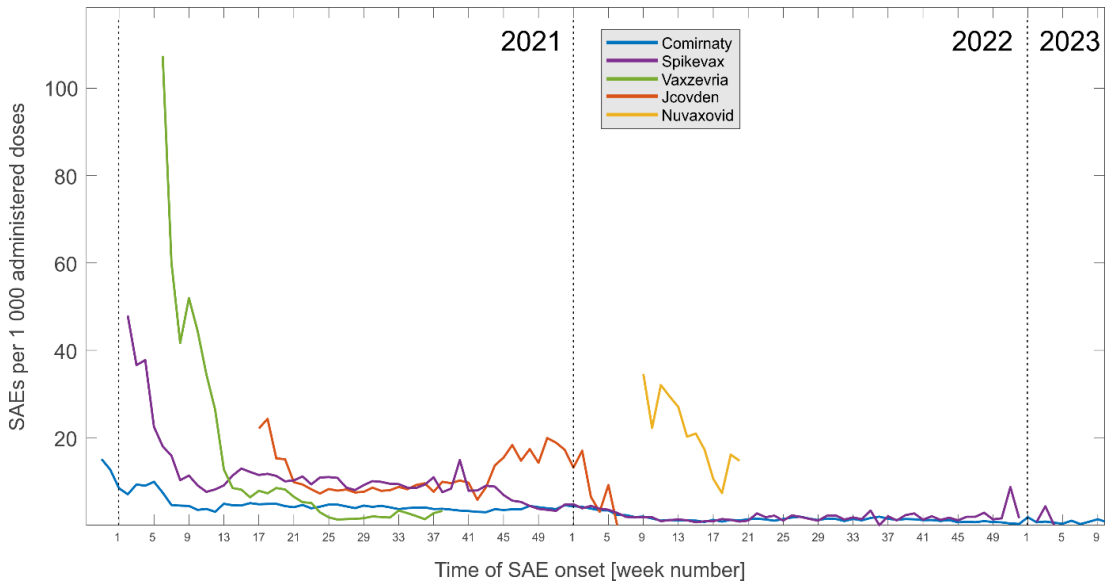

Figure 1. Weekly rates of reported suspected adverse events (SAEs). [1]Weeks in which <100 doses of a given vaccine type were administered are not shown.

Discussion

The current analysis of publicly available nationwide German SAE data revealed a pronounced and consistent temporal pattern where the three main COVID-19 vaccines exhibited very high SAE rates immediately after rollout, whereupon SAE rates fell precipitously during the first quarter of 2021. This pattern appears difficult to reconcile with non-product-related factors and is suggestive of a batch-dependent safety signal linked to the early vaccine production. Indeed, simple alternative explanations do not appear to adequately account for the observed pattern. For example, prioritized vaccination of elderly or frail individuals is unlikely to be a primary driver, since such individuals (and their care takers) typically demonstrate lower SAE reporting rates, and younger frontline healthcare workers were also amongst the first to be vaccinated. Concurrent COVID-19 infection is also an unlikely confounder, because subsequent booster campaigns, which coincided with major waves of SARS-CoV-2 virus Delta and Omicron variant infections, did not produce similar spikes in SAE rates (Figure 1). Furthermore, a decline in the willingness to report SAEs as the vaccination campaign progressed is less plausible, given that increasing vaccine hesitancy may in effect have lowered the threshold for SAE reporting. For example, SAE reporting may have increased in

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individuals who had previously reported SAEs, or those who felt coerced into vaccination, respectively.

Our findings confirm and extend preliminary reports from Denmark, Sweden, the Czech Republic, and the United States, which identified high initial SAE rates for specific, often smaller, vaccine batches, primarily for the Comirnaty modified mRNA vaccine.[1–4] The consistency of this safety signal across different countries with divergent COVID-19 vaccine policies, some of which shared the same batches with similar SAE reporting profiles, strengthens the batch-dependent safety hypothesis.[1–4,11,12] The pronounced overrepresentation of women (72% of reported SAEs) also aligns with previously published data and known effects of COVID-19 vaccination on vaginal bleeding, albeit this alone is unlikely to fully explain the magnitude of the sex disparity in SAE rates.[2,13,14]

While the rapid upscaling of COVID-19 vaccine manufacturing and global implementation of vaccination after emergency use authorization was a remarkable societal achievement, the sum of the current evidence suggests that this exceptional and expedited process may have introduced variability in early commercial vaccine batches, e.g., affecting the amount of intact mRNA, lipid nanoparticles or process-related impurities in the Comirnaty product.[15–17] Indeed, the first Periodic Safety Update Report for Comirnaty submitted by the marked authorization holder to the European Medicines Agency documented significant inter-batch variation in numbers of SAEs per dose during the initial phase of the vaccination campaign.[18] The manufacturing of the other predominant vaccine types was also subject to swift updates to facilitate large-scale production which may have introduced batch-dependent variations. Such product nonuniformity may have altered the risk-benefit profile of the agent for recipients and compromised basic principles of informed consent. Furthermore, the apparent lack of timely targeted regulatory action in response to these emergent signals is of concern, and even used under Emergency Use Authorization, changes in vaccine production, whether in scale, manufacturing process, or presentation, require approval form regulatory authorities to ensure product consistency.[6,7,19] Of note, although a recent Danish study found no differences between hospital discharge diagnoses of special interest between batches of Comirnaty with high or low reported SAE rates, that study potentially had methodological limitations and the unclear relationship between COVID-19 vaccine-associated SAEs, short-term hospitalizations, and long-term prognostic consequences, preclude definitive conclusions.[8,20]

Our study has several limitations. For example, although spontaneous reporting systems are a cornerstone of pharmacovigilance, it is well-known that such passive systems are subject to both over- and (especially) underreporting and should be viewed as hypothesis-generating systems that cannot establish causality.[21,22] Furthermore, we did not have access to information on clinical information on SAEs and data on covariates such as pre-vaccination health status, prior COVID-19, and socioeconomic data. In addition, we did not investigate potential batch-dependent efficacy.

In conclusion, we observed a sharp, early peak in SAE rates for COVID-19 vaccines in Germany that declined rapidly and remained low hereafter. This temporal pattern is consistent with a batch-dependent safety signal linked to early-production vaccines and confirms preliminary results from other countries. These findings, alongside a consistent overreporting of SAEs in women, warrant definitive, batch-level safety studies and underscore a critical need for robust, transparent quality control and proactive regulatory surveillance during rapid deployment of novel medical products.

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Data Availability Statement: The original data presented in the study are publicly available at the Paul Erlich Institute and Robert Koch Institute websites.[9,10]

Conflicts of interest: None.

References

1. Schmeling M, Manniche V, Hansen PR. Batch-dependent safety of the BNT162b2 mRNA Covid-19 vaccine. *Eur J Clin Invest* 2023 Aug; 53(8): e13998.
2. Manniche V, Schmeling M, Gilthorpe JD, et al. Reports of batch-dependent suspected adverse events of the BNT162b2 mRNA COVID-19 vaccine: Comparison of results from Denmark and Sweden. *Medicina* 2024 Aug 19; 60(8): 1343.
3. Fürst T, Šourek P, Krátká Z, et al. Batch-dependent safety of COVID-19 vaccines in the Czech Republic and comparison with data from Denmark. *Eur J Clin Invest* 2024 Oct; 54(10): e14271.
4. Jablonowski K, Hooker B. Batch-dependent Safety of the BNT162b2 mRNA COVID-19 Vaccine in the United States. *Science, Public Health Policy and the Law* 2024 Sep 26; v5.2019-2024.
5. Schmeling M, Manniche V, Hansen PR. Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine. *Eur J Clin Invest* 2023 Dec;53(12): e14102.
6. Bruce Yu B, Taraban MB, Briggs KT. All vials are not the same: Potential role of vaccine quality in vaccine adverse reactions. *Vaccine* 2021; 39(45): 6565-6569.
7. Yu YB, Briggs KT, Taraban MB. Preventive Pharmacovigilance: timely and precise prevention of adverse events through person-level patient screening and dose-level product surveillance. *Pharm Res* 2023; 40(9): 2103-2106.
8. Hviid A, Svalgaard IB. Safety of BNT162b2 mRNA COVID-19 Vaccine Batches: A Nationwide Cohort Study. *Pharmacoepidemiol Drug Saf* 2025 Sep; 34(9): e70207.
9. Paul Ehrlich Institute. https://www.pei.de/DE/arzneimittelsicherheit/pharmakovigilanz/uaw-daten/uaw-daten-node.html (accessed 24 October 2025).
10. Robert Koch Institute. COVID-19-impflugen in Deutschland. https://robert-koch-institut.github.io/COVID-19-Impfungen_in_Deutschland/ (assessed 27 November 2025).
11. Hodges R, Caperchione E, van Helden CR, et al. The role of scientific expertice in COVID-19 policy-making: Evidence from four European countries. *Public Org Rev* 2022; 33: 249-267.
12. Christensen T, Jensen MD, Kluth M, et al. The Nordic governments' responses to the Covid-19 pandemic: A comparative study of variation in governance arrangements and regulatory instruments. Regul Gov. 2022 Oct 2: 10.1111/rego.12497.
13. Blix K, Laake I, Juvet L, et al. Unexpected vaginal bleeding and COVID-19 vaccination in nonmenstruating women. *Sci Adv* 2023; 9: eadg1391.
14. Payne LA, Wise LA, Wesselink AK, et al. Association between COVID-19 vaccination and menstruation: a state of the science review. *BMJ Sex Reprod Health* 2024; 50: 212-225.
15. Kingwell K. COVID vaccines: 'We flew the aeroplane while we were still building it'. *Nat Rev Drug Discov* 2022 Dec; 21(12): 872-873.
16. Tinari S. The EMA covid-19 data leak, and what it tells us about mRNA instability. *BMJ* 2021 Mar 10; 372: n627.
17. Igyártó BZ, Qin Z. The mRNA-LNP vaccines - the good, the bad and the ugly? *Front Immunol* 2024 Feb 8; 15: 1336906.
18. Rhodes P, Parry P. Gene-based COVID-19 vaccines: Australian perspectives in a corporate and global context. *Pathol Res Pract* 2024 Jan; 253: 155030.
19. Periodic Safety Update Report 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 on 1 September 2025).

 doi:10.20944/preprints202603.0688.v1

20. Nguyen A, Schwalbe N. Apples and oranges? Can second generation vaccines become as low cost as generic medicines? *Vaccine* 2019; 37: 2910-2914.
21. 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.
22. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf* 2006; 29(5): 385-96.
23. Shimabukuro TT, Nguyen M, Martin D, et al. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 2015; 33(36): 4398-4405.