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RESEARCH LETTER

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Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine

Max Schmeling[1] | **Vibeke Manniche**[2] | **Peter Riis Hansen**[3]

[1]Innometric, Skørping, Denmark

[2]LIVA, Copenhagen, Denmark

[3]Department of Cardiology, Kobenhavns Universitet, Copenhagen, Denmark

Correspondence
Peter Riis Hansen, Department of Cardiology, Kobenhavns Universitet, Copenhagen, Denmark.
Email: prha@sund.ku.dk

To the Editor,

Vaccination has been widely implemented for mitigation of coronavirus disease-2019 (Covid-19), and by 11 November 2022, 701 million doses of the BNT162b2 mRNA vaccine (Pfizer-BioNTech) had been administered and linked with 971,021 reports of suspected adverse effects (SAEs) in the European Union/European Economic Area (EU/EEA).[1] Vaccine vials with individual doses are supplied in batches with stringent quality control to ensure batch and dose uniformity.[2] Clinical data on individual vaccine batch levels have not been reported and batch-dependent variation in the clinical efficacy and safety of authorized vaccines would appear to be highly unlikely. However, not least in view of the emergency use market authorization and rapid implementation of large-scale vaccination programs, the possibility of batch-dependent variation appears worthy of investigation. We therefore examined rates of SAEs between different BNT162b2 vaccine batches administered in Denmark (population 5.8 million) from 27 December 2020 to 11 January 2022.

Data on all SAE cases with corresponding vaccine batch labels reported to the Danish Medical Agency (DKMA) and classified by the DKMA according to SAE seriousness, and numbers of BNT162b2 doses in individual vaccine batches registered by the Danish Serum Institute, respectively, are publicly available and were retrieved upon request. The DKMA-managed spontaneous SAE reporting system accepts reports of SAEs from any source, for example healthcare providers, patients and other members of the public. SAEs are assigned Medical Dictionary for Regulatory Activities (MedDRA) terms that do not necessarily correspond to verified medical diagnoses, and more than 1 SAE may be assigned to a report. SAE seriousness was classified as non-serious, serious (hospitalization or prolongation of existing hospitalization, life-threatening illness, permanent disability or congenital malformation) or SAE-related death respectively. The study relied exclusively on the secondary use of these anonymized data and was thus exempt from research ethics board review. SAEs were counted on a batch level by linking individual SAEs to the batch label(s) of BNT162b dose(s) that the subject had received. The total number of SAEs associated with each batch was divided by the number of doses in the batch to obtain the rate of SAEs per 1000 doses. Since the observed relationship between the numbers of SAEs and BNT162b2 vaccine doses was highly heterogeneous, conventional regression statistics were not considered to be applicable. Therefore, heterogeneity in the relationship between the numbers of SAEs and doses per vaccine batch was assessed by log-transformation followed by non-hierarchical cluster analysis and general linear model (GLM) test for differences in SAE rates between batches. Reporting of the study conforms to broad EQUATOR guidelines.[3]

[Correction added on 13 April 2023, after first online publication: The corresponding author's affiliation was updated in this version]

A total of 10,793,766 doses were administered to 4,026,575 persons with the use of 52 different BNT162b2 vaccine batches (2340–814,320 doses per batch) and 43,496 SAEs were registered in 13,635 persons, equaling 3.19 ± 0.03 (mean ± SEM) SAEs per person. [Correction added on 09 June 2023, after first online publication: The total number of doses and patient counts were corrected in the preceding statement]. In each person, individual SAEs were associated with vaccine doses from 1.531 ± 0.004 batches resulting in a total of 66,587 SAEs distributed between the 52 batches. Batch labels were incompletely registered or missing for 7.11% of SAEs, leaving 61,847 batch-identifiable SAEs for further analysis of which 14,509 (23.5%) were classified as severe SAEs and 579 (0.9%) were SAE-related deaths. Unexpectedly, rates of SAEs per 1000 doses varied considerably between vaccine batches with 2.32 (0.09–3.59) (median [interquartile range]) SAEs per 1000 doses, and significant heterogeneity ($p < .0001$) was observed in the relationship between numbers of SAEs per 1000 doses and numbers of doses in the individual batches. Three predominant trendlines were discerned, with noticeable lower SAE rates in larger vaccine batches and additional batch-dependent heterogeneity in the distribution of SAE seriousness between the batches representing the three trendlines (Figure 1). Compared to the rates of all SAEs, serious SAEs and SAE-related deaths per 1.000 doses were much less frequent and numbers of these SAEs per 1000 doses displayed considerably greater variability between batches, with lesser separation between the three trendlines (not shown).

The observed variation in SAE rates and seriousness between BTN162b2 vaccine batches in this nationwide study was contrary to the expected homogenous rate and distribution of SAEs between batches. In Denmark and other EU/EEA countries, vaccine quality is monitored according to Official Control Authority Batch Release (OCABR) guidelines and to our knowledge, potential differences in BNT162b2 vaccine batch clinical safety or effectiveness have not been reported previously, for example in pre-authorization trials and subsequent population-based studies.[4,5] Such effects may be easier to detect in small countries like Denmark where BNT162b2 vaccines during the study period were generally provided in several smaller batches. Also, regulatory monitoring and scientific interest in COVID-19 vaccine safety have primarily focused on serious adverse events, for example myocarditis.[6] In any case, identification of such effects evidently requires that observed adverse events are linked with the respective individual batch labels and sizes (dose numbers). Previously, variation in the

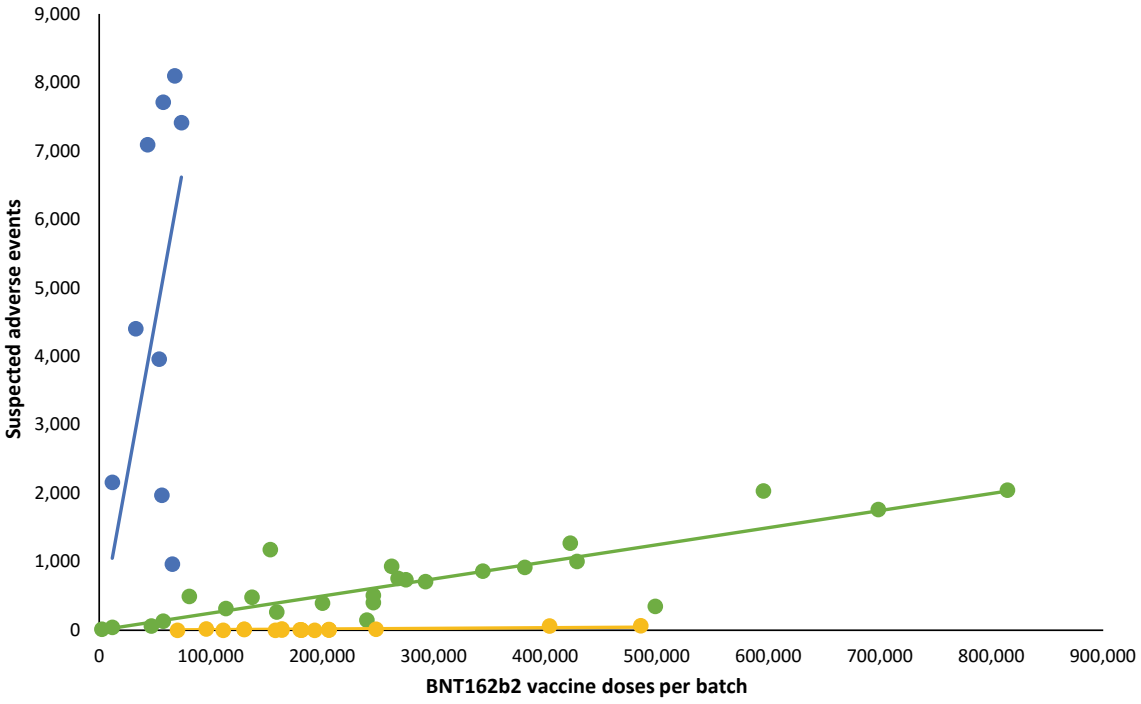

FIGURE 1 Numbers of suspected adverse events (SAEs) after BNT612b2 mRNA vaccination in Denmark (27 December 2020–11 January 2022) according to the number of doses per vaccine batch. Each dot represents a single vaccine batch. Trendlines are linear regression lines. Blue: $R^2 = 0.78$, $\beta = 0.0898$ (95% confidence interval [CI] 0.0514–0.1281), green: $R^2 = 0.89$, $\beta = 0.0025$ (95% CI 0.0021–0.0029), yellow: $R^2 = 0.68$, $\beta = 0.000087$ (95% CI 0.000056–0.000118). Vaccine batches representing the blue, green and yellow trendlines comprised 4.22%, 63.69% and 32.09% of all vaccine doses, respectively, with 70.78%, 27.49% and 47.15% (blue trendline), 28.84%, 71.50% and 51.99% (green trendline), and 0.38%, 1.01%, and 0.86% (yellow trendline) of all SAEs, serious SAEs, and SAE-related deaths, respectively.

production (culture growth) of the Bacille Calmette-Guérin vaccine has been shown to influence important immunological effects of this vaccine,[7] and two cases of myocarditis have been reported in two young males after receiving mRNA-1273 COVID-19 vaccine (Moderna) from the same vaccine batch on the same day.[8] Indeed, variations (batch-to-batch, vial-to-vial and even dose-to-dose) in vaccines may occur as a result of variabilities and practice breaches in, for example vaccine manufacturing, storage, transportation, clinical handling and control aspects, and in 2021, three lots of the mRNA1273 vaccine totalling more than 1.6 million doses were recalled in Japan after 39 vials of the vaccine were found to contain foreign materials.[9] Leaked and contested data have also suggested that some early commercial batches of the BNT162b2 vaccine contained lower than expected levels of intact mRNA.[10]

The present preliminary findings must be interpreted in the light of several limitations. The DKMA-managed spontaneous SAE reporting system in Denmark is a passive surveillance system akin to the Vaccine Adverse Event Reporting System (VAERS) in the US, and reports from these systems are subject to reporting biases, with potential for both under- and over-reporting, as well as incomplete data and variable quality of the reported information.[11,12] Owing to these inherent limitations, signals detected by these systems must be considered to be hypothesis-generating and generally cannot be used to establish causality.[11–14] In addition, in the present study, the SAE case history of prior COVID-19 was unknown, and specific SAE types (MedDRA system organ class etc.), demographics of SAE cases, relationships of SAEs with consecutive vaccine doses in individuals cases, temporal trends in the observed batch-dependency of SAEs, and batch-dependent effects on vaccine effectiveness, respectively, were not examined. Notably, to our knowledge, the Danish Serum Institute has not issued recalls of BNT162b2 vaccine batches. In conclusion, the results suggest the existence of a batch-dependent safety signal for the BNT162b2 vaccine, and more studies are warranted to explore this preliminary observation and its consequences.

CONFLICT OF INTEREST STATEMENT

None.

ORCID

Peter Riis Hansen https://orcid.org/0000-0002-9056-535X

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