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Batch-dependent Safety of the BNT162b2 mRNA COVID-19 Vaccine in the United States

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Research Letter

This research letter adds to a recent publication from Schmeling, Manniche, and Hansen (2023) [1] that identified unexpected, batch-dependent suspected adverse events (SAEs) following Pfizer's BioNTech's BNT162b2 mRNA COVID-19 vaccination (Pfizer-BioNTech). The study associated vaccine lot dose allocations with SAEs rates from data collected in Denmark between 12/27/20 and 1/11/22. The researchers classified SAEs from case data into three categories (i.e., death, serious, and all SAEs). Three distinct clusters were identified that exhibit different rates of lot size to SAEs (i.e., yellow, green, and blue). The researchers found that the larger the vaccine lot size, the lower the SAEs rates (identified as the yellow clusters), and vice versa (i.e., smaller lot sizes correlate with higher SAEs rates, or blue clusters). Comparing the Denmark results with the United States (U.S.) would determine if similar patterns exist with a larger population as compared to Denmark (i.e., 11 million vaccinated in Denmark [1] versus 410 million Pfizer-BioNTech vaccination doses distributed through 2022 in the U.S. [2]). This study uses Pfizer-BioNTech vaccine allocation dose data and SAE case data available through the Vaccine Adverse Event Reporting System (VAERS) [3] to identify associations between doses allocated and SAEs. To be consistent, the same methodology was used to identify the same three clusters for the U.S. In addition to comparing with the Denmark cluster results, this study identified SAE outliers and their geospatial distribution by type of organization (i.e., hospitals, universities, and mass vaccination health department sites) organized through health departments.

In the United States, 52.8 percent of all COVID-19 vaccinations allocated were the Pfizer-BioNTech vaccine [4]. A Freedom of Information Act (FOIA) request to the U.S. Centers for Disease Control (CDC) that contain vaccine doses by lot numbers was publicly released through legal action in October 2022 [2]. From this data, over 410 million doses of the Pfizer-BioNTech vaccine were allocated between 12/13/20 and 4/26/22 from 156 different lot numbers [2]. This data set includes vaccination lot number, vaccine provider (with name, city, state, and zip), number of doses per shipment, order shipped date, and lot expiration date for shipments made across the U.S. Within the study period, 46,327 different vaccine providers received shipments of Pfizer-BioNTech vaccines. Six lots were excluded from the study as allocations likely continued past the study end date (see Supplemental Table 1). Also note that 28,170

doses, or 0.01 percent, had reported missing lot numbers.

Geographically, approximately 52 percent of Americans were vaccinated in a pharmacy or grocery store, approximately 25 percent were vaccinated in a medical facility (i.e., doctor's office, medical clinic, or urgent care), and approximately 12 percent of vaccinations were distributed to health departments who primarily ran mass vaccination sites. The remaining vaccinations were sent to universities, colleges, and government agencies (e.g., fire and emergency departments). On average, 1,011,055 vaccines (CI: 916,807-1,105,302) were distributed each day, ranging between 1 and 10 lots, with an average of 4.3 different lots (CI: 4.1, 4.5) distributed per day. It was hypothesized that larger and fewer lot sizes were manufactured as the pandemic commenced, but this is not the case. In fact, a slight increase in the total number of lots by day was calculated. The total number of doses per lot ranged from 10,530 to over 11.8 million. On average, vaccine lots contained 2.6 million doses (CI: 2.3 to 2.9). Three of the lots are high outliers (FL0007, FK5127, and FK5618 with 11.8, 10.6, and 8.9 million doses in each lot, respectively). Outliers in this study are defined as having z-scores over three standard deviations. Weekly distributions of the vaccine are seasonal with a general decline as shown on Figure 1a. The lot distribution number of days distributed varied with some lots being distributed on one day where others were distributed over the course of 100 days. The total vaccines distributed, the first and last shipment of each lot, and the monthly allocations are provided in Supplemental Table 1.

SAEs in this study were identified in VAERS, a passive reporting system similar to the reporting system used in the Denmark study [1]. Calendar years 2020, 2021, and 2022 were obtained for all reports, including lot number, state, and worst outcomes associated with the Pfizer-BioNTech COVID-19 vaccination. Note that the VAERS system provides a write-in field for lot number, so the lots were reclassified using the protocol set forth in a similar study conducted by Ceacareanu and Wintrob (2021) [5]. For the three years of data, a total of 977,542 cases were reported to VAERS. Of these, 455,820 cases (46.7 percent) were associated with the Pfizer BioNTech vaccination (see Supplemental Table 2 for reported injury classes by vaccine lot). From these data, 322,237 (29 percent) had a lot number and of these, 310,799 were discernible with 194 different lot numbers. For this study, 290,835 SAEs aligned with the 150 vaccine lot numbers identified in the Pfizer-BioNTech allocation data. The worst-case outcome was identified for each case so as not to double count individual cases. Overall, the number of reported SAEs has declined through time in all categories consistent with a decrease in VAERS reports (Figure 1a-1c) due to system management, or fewer sufferers who report, or fewer sufferers. Also note that VAERS reports continued through December 2022 (and likely beyond) even though vaccinations from the study lot ended in April 2022. From this data, 78 percent of all SAEs were not serious, 20 percent were serious (defined in this study as requiring hospitalization or an emergency room/department visit or reporting a life-threatening event, permanent disability, or congenital malformation event), and 2 percent of the reports resulted in death. VAERS makes the initial report available. Consequently, if a condition escalated in severity and the report was updated, that update is not made available to the public and would not be reflected in this study. It would be expected that SAE reports would trend with population with the most SAE reports in California, Texas, Florida, and New York (the most populated states in the nation); however, an unexpectedly high number of deaths were reported in Tennessee and Kentucky (Figure 2a). The proportions of SAEs

by injury class in each state with relatively higher death and serious injury (pink and blue) in Illinois, Michigan, Minnesota, and Wyoming is shown in Figure 2b. South Dakota, Kentucky, and Tennessee are outliers for high death rates as a proportion.

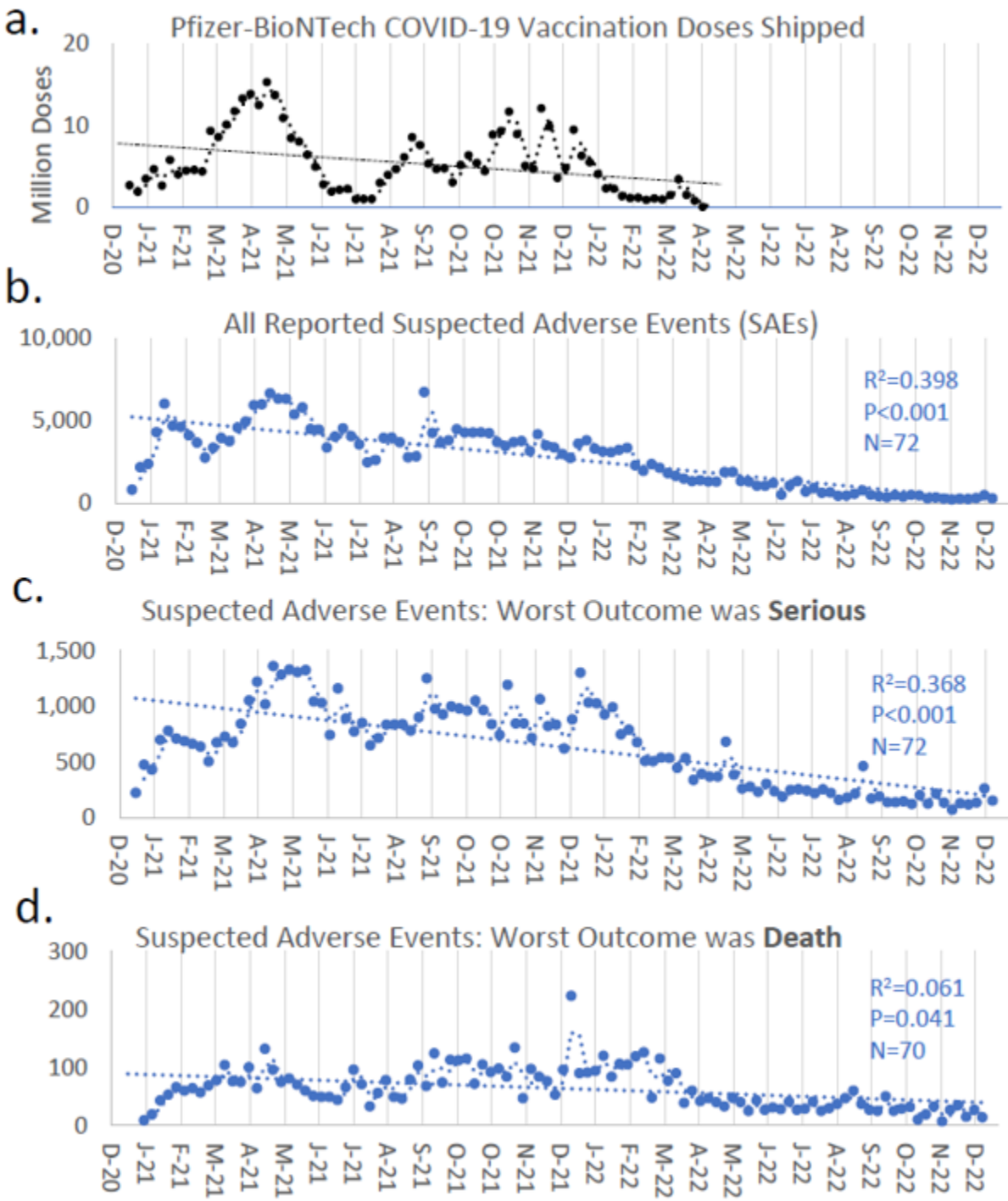

Figure 1. Pfizer-BioNTech COVID-19 Vaccination and Suspected Adverse Events (SAEs) Timeline. Weekly doses allocation (a.), all reported SAEs by week (b.), and work outcome was serious or a reported death by week (c. and d., respectively). SAEs reported from Vaccine Adverse Event Reporting System (VAERS) Injury. Reported correlations in blue are between doses shipped and all SAEs and worst outcomes for serious injuries and deaths.

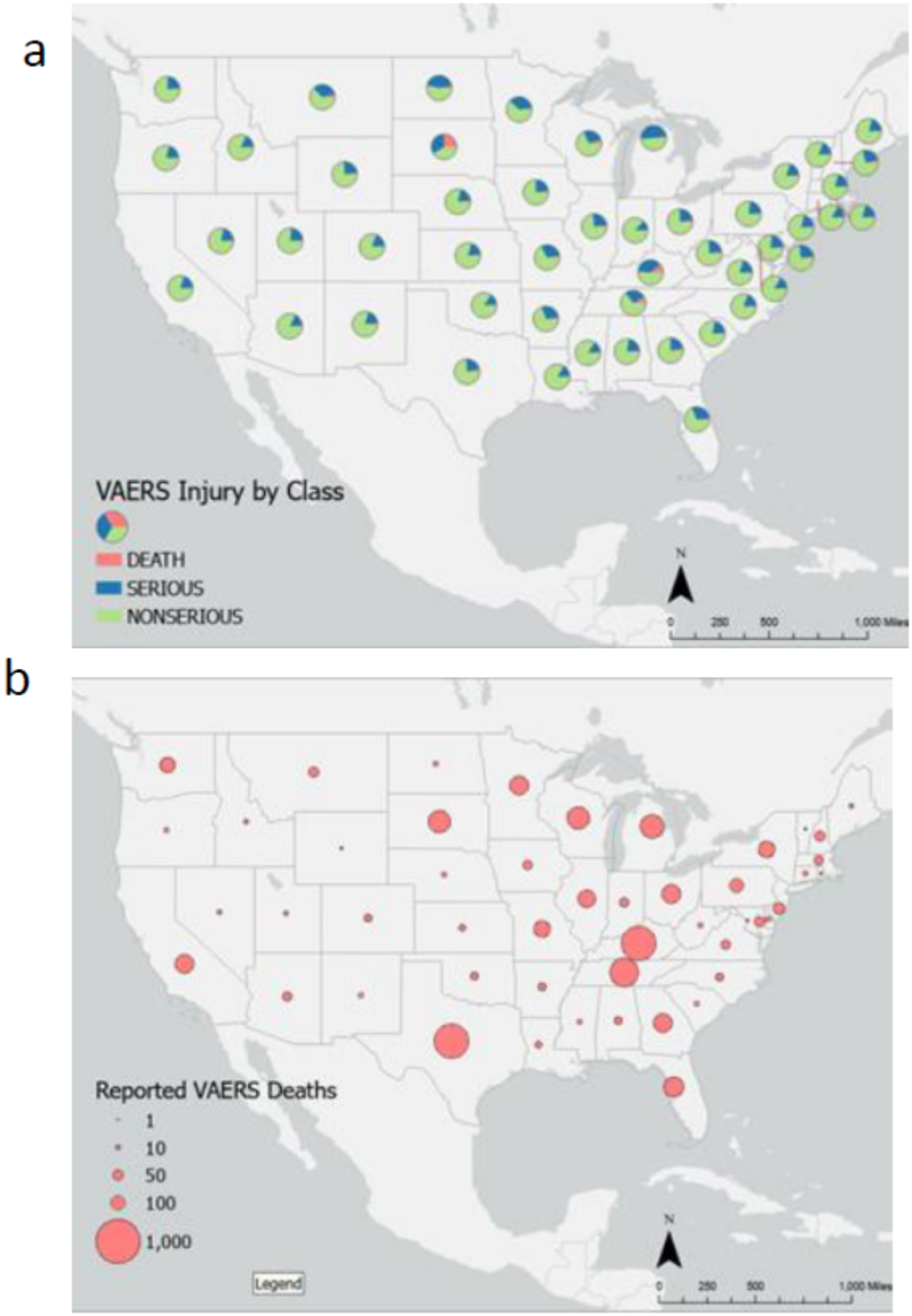

Figure 2. Suspected Adverse Events After Pfizer-BioNTech COVID-19 Vaccination Reported from the Vaccine Adverse Event Reporting System (VAERS) in the United States (2020-2022). Percent of VAERS report by VAERS type (a), total reported VAERS deaths by state (b)

Variable	Doses Allocated	All SAEs	Death SAEs	Serious SAEs	Incidence**** of All SAEs	Incidence of Death	Incidence of Serious SAE
Descriptive Statistics							
Totals	394,311,470*	290,835***	6,705	67,715	-	-	-
Mean	2,628,743	1,939	45	451	1,010	27	229
Mean CI*	2,382,804, 2,874,682	1,781, 2,097	37, 52	407, 496	851, 1,168	21, 33	195, 263
Minimum	10,530	4	0	0	95	0	0
Maximum	11,777,900	4,524	249	1,257	5,167	164	1,041
Standard Deviation	1,524,346	980	48	278	981	38	208
Correlations for Total and Clusters							
Total Allocations	R Square (p-value)	0.018 (.102)	**0.046 (.008)**	0.000 (.857)	**.232 (<.001)**	**.200 (<.001)**	**.228 (<.001)**
	Beta (CI)	209 (-41, 459)	-6,759 (-11,750, -1,769)	-81 (-970, 808)	-728 (-969, -527)	-17,977 (-23,825, -12,129)	-3,488 (-4,532, -2,444)
Yellow Cluster (n=29)	2,864,647	31,885 (11%)	212 (3.2%)	4,647 (6.9%)	-	-	-
	R Square (p-value)	**.758 (<.001)**	.001 (.889)	**.289 (.003)**	.074 (.155)	**.195 (.017)**	**.465 (<.001)**
	Beta (CI)	3,253 (2,526, 3,980)	-15,978 (-248,431, 216,476)	25,136 (9,579, 40,692)	-7,803 (-18,740, 3,134)	-990,677 (-1,787,817, -193,537)	-100,977 (-143,759, -58,194)
Green Cluster (n=76)	217,713,150	144,000 (49.6%)	2,204 (32.9%)	34,036 (50.3%)	-	-	-
	R Square (p-value)	**.369 (<.001)**	**.160 (<.001)**	**.323 (<.001)**	.048 (.057)	.004 (.590)	.017 (.266)
	Beta (CI)	611 (426, 796)	15,293 (7,190, 23,395)	1,963 (1,304, 2,622)	-723 (-1,470, 24)	7,789 (-20,860-36,438)	1,628 (-1,264, 4,519)
Blue Cluster (n=41)	65,200,200	114,463 (39.4%)	4,289 (64.0%)	28,942 (42.8%)	-	-	-
	R Square (p-value)	**.297 (<.001)**	**.253 (<.001)**	**.731 (<.001)**	**.441 (<.001)**	**.278 (<.001)**	**.460 (<.001)**
	Beta (CI)	546 (273, 818)	8,753 (3,876, 13,629)	2,985 (2,398, 3,572)	-513 (-700, -326)	-12,153 (-18,499, -5,808)	-3,379 (-4,565, -2,194)

*410,352,400 doses in 156 lots were allocated between December 15, 2020 through April 26, 2022. Of these, 28,170 allocations did not identify a lot number. *Lots FL8094, FL8095, FM0173, FM7553, FM9992, and FP4554 were excluded since these lots had allocations on the last day of the data set and it is unknown if further allocations were made after this date. ***Reported SAES obtained from VAERS. Total Pfizer BioNTech SAEs were 455,820 (2020 through 2022); 322,237 SAEs had a lot number associated with the record; however, 310,799 records from 194 lots were discernable through the end of December 2022. ****Incidence of SAEs reported per 1,000,000 doses allocated. *Confidence interval at 95% SAE=Suspected Adverse Event, alpha at 0.05.

Table 1. Pfizer-BioNTech COVID-19 Vaccine Allocations and Suspected Adverse Events (SAEs) Statistics Summary

Summary statistics presented in Table 1 indicate that on average 1,939 SAEs (CI: 1,781, 2,097) were reported for each lot number with a range between 4 and 4,527. Cases of death and serious SAEs resulted on average 45 deaths (CI: 37, 52) and 451 SAEs (CI: 407, 496) per vaccine lot (Table 1). Three lots did not record any deaths or serious SAEs (i.e., FD7220, FL4211, and P000133) all of which had shipments occurring on one single day (10,530 doses shipped on Oct 19, 2021; 15,800 doses shipped on Feb 23, 2022; and, 63,180 doses shipped on Jan 3, 2022, respectively). One additional vaccine lot (FJ9943) also did not result in any reports of death but had cases of serious and non-serious SAEs; however, this lot was much larger with 1,745,400 doses distributed over 43 days (February 16, 2022 to March 31, 2022). No low statistical outliers were identified in any of the variables analyzed in this study; however, high outliers were discovered in all three categories of SAEs, but mostly for different lot numbers. Five lots had high outliers for death (i.e., EL0140, EL9261, EL3248, EN9581, and EJ1686); four for serious (EK4176, EK5730, EH9899, and EJ1685), and five for ALL SAEs (EK5730, EH9899, EK4176, EK9231, and EJ1685). These vaccinations were the first to be distributed in December 2020 and early 2021. The identified outliers per 10,000 doses allocated identified in VAERS were mapped at the regional level (Figure 3a). The geospatial pattern was found to be clustered (Global Moran's I = .081, z-score=3.76, p=<.001) with the highest distribution of outlier rate being distributed in regions that would be expected, like in large population centers. High outlier distribution clusters by region (see

Supplemental Table 4) identified using Anselin's Local Moran's I Statistic [6] identified high outlier clusters (shown in pink and red on Figure 3b) in over a dozen states. Over 5 percent of the vaccination lots that resulted in the most VAERS death reports were distributed to government agencies, 4.7 percent distributed to hospitals, 4.7 percent to universities, and 4.5 percent to health departments, mostly mass vaccination sites. Less than 2 percent of the first vaccinations were allocated to first responder agencies (e.g., municipal fire and emergency departments). With over half of vaccinations distributed to pharmacies and large grocery chains, there was a surprisingly low rate of death outliers allocated to these locations. A progression through time, from blue clusters (which had the most deaths and serious injuries) to green and yellow clusters, indicate that the first batches of vaccine resulted in more injuries than later vaccines that were sent to pharmacies and grocery stores (see Supplemental Table 1).

The relationship between lot size and SAEs (Table 1 and Figure 4) was hypothesized to correlate positively and significantly (namely, that larger lot sizes would result in larger SAEs); however, they do not ($R2=.018$, $p=.102$) (Figure 4a). However, the relationship between lot size and the incidence of all SAEs (per million doses) showed a weak but significant negative correlation (i.e., $R2=.232$, $p<.001$). To be consistent with the Denmark study, three clusters (yellow, green, and blue) were identified using hierarchical clustering in SPSS using log transformed data for both total reported SAEs and the total number of SAEs per million people (Figure 4b). The incidence of SAEs was negatively and significantly correlated in all three clusters (i.e., yellow $R2=.758$, green $R2=.369$, and blue $R2=.297$, all $p<.001$). The highest blue cluster, which represents the most injurious, representing 64 percent of all death reports, 43 percent of all serious injury reports, and 39 percent of all SAE reports were weakly significant in all variables with stronger significance ($R2=.731$, $p>.001$) between lot size and serious injury. Using state aggregated data (see Supplemental Table 3), statistically significant correlations between total allocations and all SAEs, deaths, and serious events indicated a dose response pattern for overall SAEs, serious injury, and death reports ($R2=.955$, $p<.001$, $R2=.275$, $p<.001$, and $R2=.673$, $p<.001$, respectively) (Table 1).

In conclusion, the batch-dependent trend in the U.S. is similar to trends in Denmark with some differences. Specific lot data is not directly comparable since different lots were allocated in the U.S.; however, a comparison using the same methodology provided similar results, namely that three clear clusters emerged. In general, U.S. data follows the same pattern however, in this study, all three clusters have slightly negative beta coefficients (decreasing SAEs with increasing lot size) where the Denmark study showed slightly positive (increasing SAEs with increasing lot size) (see Figure 4). The highest SAEs rates were identified in vaccine batches allocated in the first two months of the vaccination program, fitting squarely into the blue category, with the highest proportions being sent to government agencies, hospitals, universities, and health departments.

Data quality problems have been well documented from the Pfizer-BioNTech vaccine. Tinari (2021) [7] documents a December 2020 leak of classified Pfizer documents from European Medicines Agency (EMA) scientists who found emails regarding "truncated and modified mRNA species present in the finished product" and that "commercial manufacturing was not producing vaccines to the specifications expected" [7]. In this study, there is a higher rate of

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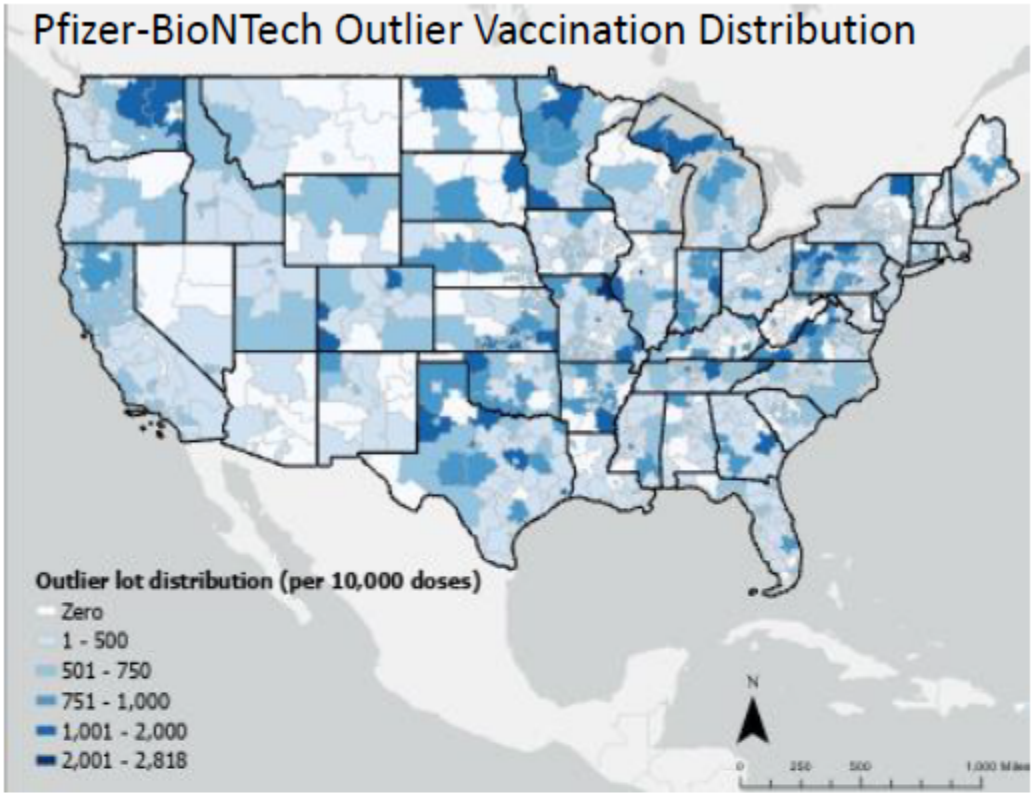

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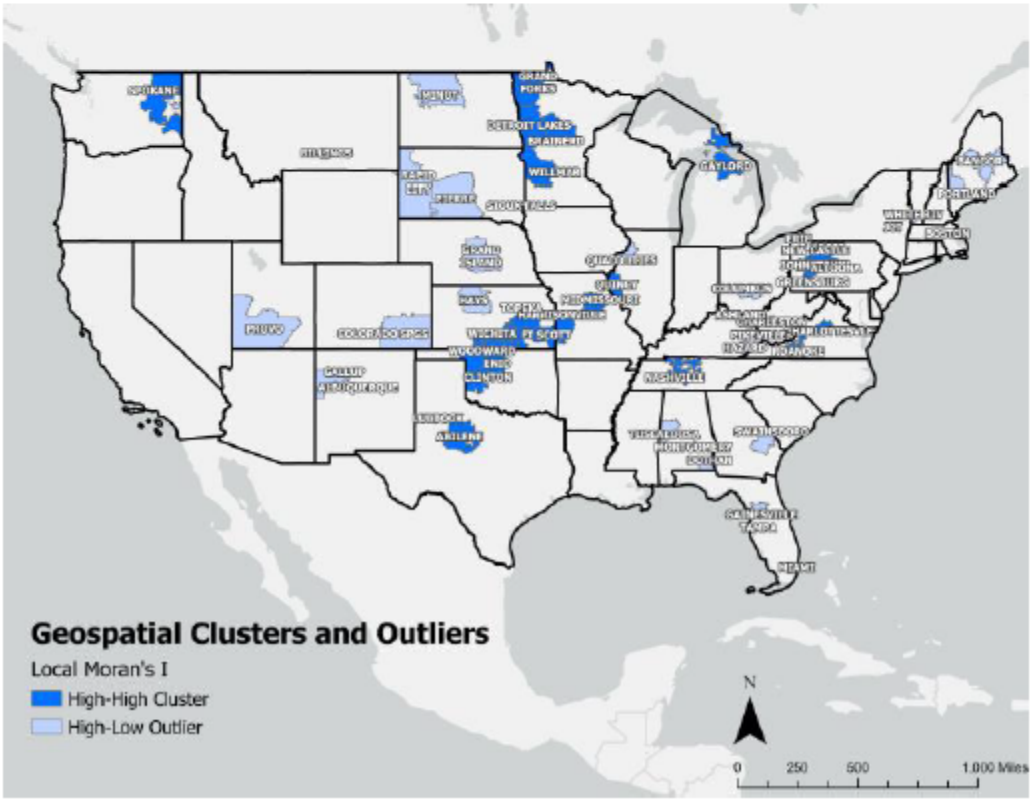

Figure 3. Geospatial distribution of Pfizer-BioNTech Outlier Vaccinations by Region (a) Geospatial Clusters and Outliers by Region (b)

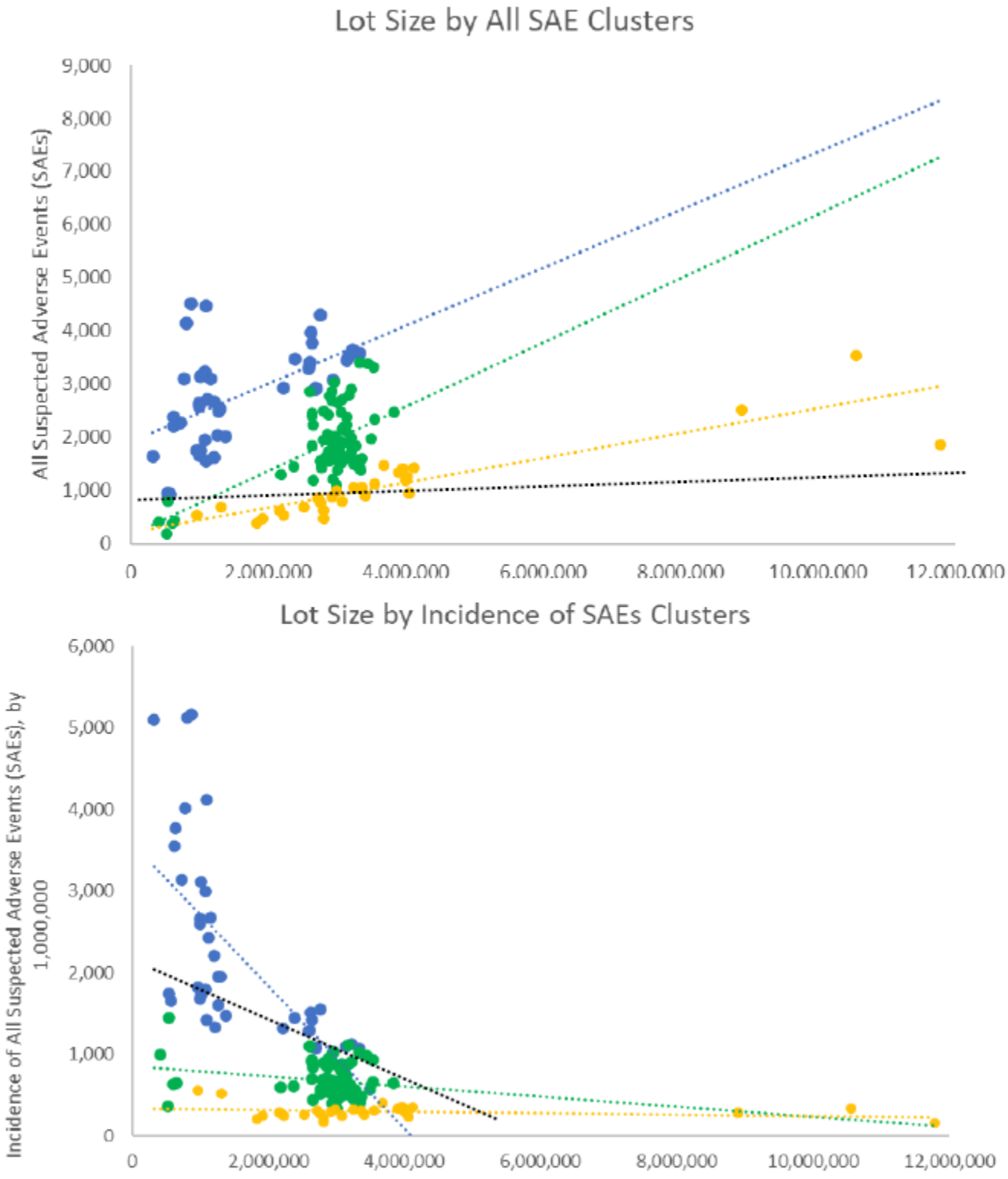

Figure 4. Relationship between Pfizer-BioNTech vaccination doses and Suspected Adverse Events (SAEs) (a. All SAEs; b. Incidence of SAEs (per 1,000,000 doses)

VAERS reports in the first month which could be explained by the noted manufacturing errors. Bruce, Taraban, and Briggs (2021) [8] describes the system of quality control currently being conducted at the batch level. They used reported cases of anaphylactic reactions from different batches, identified differences in manufacturing, and concluded that while defects in vaccination batches are caught before filling the vials, quality control is lacking at the vial-level. Missing data is also a limitation. Ceacareanu and Wintrob [5] used the VAERS system to associate lot numbers with adverse events from all vaccines through May 2021. They found that 33.54 percent of total lots were missing in the data set. This study found that 11 percent of the lot numbers were missing in the Pfizer-BioNTech-specific VAERS reports; however, approximately 20 percent of the lots were missing for both death and serious reports of injuries. The Denmark study identified only 7 percent missing lot numbers [1]. This data gap could easily be addressed by requiring the selection of a lot number from a dropdown menu in VAERS, as this information is known in advance. Pfizer COVID-19 vaccines are manufactured at over 20 sites around the world [9]. However, no public information is published that identifies which batches are manufactured at which facility. Thus, identifying the cause of the higher vaccine injury rates by lot would be difficult without this information.

Several years after one of the, if not the, largest pharmaceutical roll-out in human history, there remain many unknowns and unknowables. Which vaccines shipped actually went into an arm? How did administration training differ by service and geography? Was appropriate time given for aspiration of the needle (5 to 10 seconds), and slowly enough to allow the deltoid muscle fibers to expand and retain the injection (10 seconds per milliliter)? How do VAERS classifications align with medical diagnoses? And of course, what is the true differential under-reporting factor? These are just the basics for understanding outcome and none of these are known, which is a disservice to pharmacovigilance and undercuts every statement of safety.

This study, like the Denmark study, concludes that there were clear variations in Pfizer-BioNTech's vaccine lots and that the same pattern of SAEs was observed. The vaccination allocation data used in this study was only released through a forced legal action and does not provide data past April 2022. At present, the VAERS public data set is only provided at the state level which is insufficient to capture variations in different regions within a state. Automatically providing updated and democratized data publicly would improve transparency and trust in government.

References

1. Schmeling M, Manniche V, and Hansen PR. Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine. Eur J Clin Invest. 2023;e13998. https://doi.org/10.1111/eci.13998

2. Pfizer allocation data link and press release https://icandecide.org/article/pfizer-lot-dose-documents/
https://icandecide.org/press-release/update-ican-obtains-additional-and-more-complete-pfizer-vaccine-lot-dose-and-distribution-data/

3. US Department of Health and Human Services, Vaccine Adverse Event Reporting System. https://vaers.hhs.gov/data.html

4. CDC (May 11, 2023) COVID-19 Vaccinations in the United States, Jurisdiction. https://data.cdc.gov/Vaccinations/COVID-19-Vaccinations-in-the-United-States-Jurisdi/unsk-b7fc/about_data

5. Ceacareanu AC, Wintrob ZA. Summary of

COVID-19 vaccine-related reports in the Vaccine Adverse Event Reporting System. J Res Pharm Pract.2021;10:107-13.

6. Anselin, L. (1995) "The Local Indicators of Spatial Association – LISA", Geographical Analysis, 27: 93-115.

7. Tinari S. The EMA covid-19 data leak, and what it tells us about mRNA instability. BMJ.2021;372:1-3.

8. Bruce YY, Taraban MB, Briggs KT. All vials are not the same: potential role of vaccine quality in vaccine adverse reactions. Vaccine.2021;39:6565-6569.

9. Pfizer COVID-19 Scaled Up Manufacturing Fact Sheet, dated 10/18/22, https://cdn.pfizer.com/pfizercom/How_Pfizer_Scaled_Up_Manufacturing_Covid19_10182022.pdf

Supplementary Files

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