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Tree-based data mining for safety assessment of first COVID-19 booster doses in the Vaccine Safety Datalink

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ABSTRACT

Background: The Centers for Disease Control and Prevention's Vaccine Safety Datalink (VSD) has been performing safety surveillance for COVID-19 vaccines since their earliest authorization in the United States. Complementing its real-time surveillance for pre-specified health outcomes using pre-specified risk intervals, the VSD conducts tree-based data-mining to look for clustering of a broad range of health outcomes after COVID-19 vaccination. This study's objective was to use this untargeted, hypothesis-generating approach to assess the safety of first booster doses of Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273), and Janssen (Ad26.COV2.S) COVID-19 vaccines.

Methods: VSD enrollees receiving a first booster of COVID-19 vaccine through April 2, 2022 were followed for 56 days. Incident diagnoses in inpatient or emergency department settings were analyzed for clustering within both the hierarchical ICD-10-CM code structure and the follow-up period. The self-controlled tree-temporal scan statistic was used, conditioning on the total number of cases for each diagnosis. P-values were estimated by Monte Carlo simulation; p = 0.01 was pre-specified as the cut-off for statistical significance of clusters.

Results: More than 2.4 and 1.8 million subjects received Pfizer-BioNTech and Moderna boosters after an mRNA primary series, respectively. Clusters of urticaria/allergy/rash were found during Days 10–15 after the Moderna booster (p = 0.0001). Other outcomes that clustered after mRNA boosters, mostly with p = 0.0001, included unspecified adverse effects, common vaccine-associated reactions like fever and myalgia, and COVID-19. COVID-19 clusters were in Days 1–10 after booster receipt, before boosters would have become effective. There were no noteworthy clusters after boosters following primary Janssen vaccination.

Conclusions: In this untargeted data-mining study of COVID-19 booster vaccination, a cluster of delayed-onset urticaria/allergy/rash was detected after the Moderna booster, as has been reported after Moderna vaccination previously. Other clusters after mRNA boosters were of unspecified or common adverse effects and COVID-19, the latter evidently reflecting immunity to COVID-19 after 10 days.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; VSD, Vaccine Safety Datalink.

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1. Introduction

The U.S. Centers for Disease Control and Prevention (CDC)'s Vaccine Safety Datalink (VSD), a collaboration between CDC and 9 integrated healthcare organizations with a 30-year history of conducting rigorous vaccine safety research [1], has played a prominent role in surveillance for the safety of COVID-19 vaccines in the United States. Starting immediately after the Food and Drug Administration (FDA) issued the first Emergency Use Authorization for a COVID-19 vaccine in December 2020, VSD began sequential analysis in its population of more than 12 million to determine on a weekly basis whether risks of any of 23 outcomes increased after COVID-19 vaccination [2]. The results of VSD's surveillance have been presented to the Advisory Committee on Immunization Practices (ACIP) on numerous occasions, informing U.S. vaccine policy [2–6]. In addition to conducting surveillance for pre-specified health outcomes, VSD has been using a population-based data-mining approach to look for possible associations between receipt of a COVID-19 vaccine and any of an extremely broad range of medically attended adverse events [7].

On September 24, 2021, the CDC recommended a booster dose of the Pfizer-BioNTech (BNT162b2) COVID-19 vaccine at least 6 months after the Pfizer-BioNTech primary series for people aged ≥ 65 years, residents of long-term care facilities, and people aged 50–64 years with certain underlying medical conditions [8]. On October 21, 2021, the CDC expanded this recommendation, stating that the above groups as well as those aged ≥ 18 years with underlying medical conditions or working or living in high-risk settings were eligible for a booster dose of Pfizer-BioNTech, Moderna (mRNA-1273), or Janssen (Ad26.COV2.S) COVID-19 vaccine. The recommended timing to receive a booster dose for those having received an mRNA primary series was at least 6 months later; the recommended booster timing for those having received the Janssen primary vaccination was at least 2 months later [9]. A month later, on November 19, 2021, the CDC recommended booster shots for all adults aged ≥ 18 years [10]. The CDC expanded the recommendation to receive a booster dose to adolescents aged 16–17 years (at least 6 months after the primary series) on December 9, 2021 [11] and further expanded the recommendation to cover all those aged 12–17 years (at least 5 months after the primary series) on January 5, 2022 [12]. Only the Pfizer-BioNTech vaccine was authorized for use as the primary series or booster dose in adolescents at that time. On December 16, 2021, on the basis of updated vaccine effectiveness and safety data, the ACIP made a preferential recommendation for the use of mRNA COVID-19 vaccines over the Janssen vaccine [13].

In the current report, we describe the results of VSD's application of a tree-based data-mining method to study the safety of Pfizer-BioNTech, Moderna, and Janssen first booster doses.

2. Methods

2.1. Study population

The study population consisted of recipients of first boosters of COVID-19 vaccines who were enrolled at a VSD site from their primary COVID-19 vaccine series through 56 days after their first booster. COVID-19 boosters administered through April 2, 2022 were included.

Analyses were conducted for all ages combined, as well as for the following age groups for which the respective vaccine was authorized or approved: ages < 18 (only for Pfizer-BioNTech), 18–39, 40–64, and ≥ 65 years.

2.2. COVID-19 vaccine exposure and follow-up

Analyses of four types of booster vaccinations were conducted: (1) the first Pfizer-BioNTech (ascertained by CVX codes 208, 217, and 218) received at least 5 months after at least 2 doses of any mRNA vaccine, (2) the first Moderna (CVX code 207) received at least 5 months after at least 2 doses of any mRNA vaccine, (3) the first mRNA vaccine (either Pfizer-BioNTech or Moderna) received at least 2 months after at least 1 dose of Janssen vaccine (with no record of any previous mRNA vaccination), and (4) the first Janssen (CVX code 212) received at least 2 months after at least 1 dose of Janssen vaccine (with no record of any mRNA vaccination). We followed people receiving any of these 4 booster types for 56 days.

The specification in these definitions that *at least* 2 previous doses of an mRNA vaccine or *at least* one previous dose of Janssen vaccine must have been received was adopted so as not to exclude people with duplicate vaccination records, given that duplication can occur, especially when immunization registry data are integrated with vaccination data from patients' electronic health records. The timing of the booster recommendations (fall 2021), the last date of vaccinations included (April 2, 2022), and the specification to capture the first instance of vaccination at least 5 months after previous mRNA vaccination or at least 2 months after previous Janssen vaccination together ensure that the doses identified as "first boosters" were in fact almost entirely true first booster doses rather than third doses of the primary series in people who were immunocompromised or subsequent (second or third) booster doses.

2.3. Hierarchical diagnosis tree and outcomes of interest

We identified outcomes using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. ICD-10-CM codes have a hierarchical tree-like structure, starting with 21 broad categories of diagnoses, for example, diseases of the musculoskeletal system and connective tissue, which progressively branch into more and more specific sets of diagnoses, culminating in highly specific diagnosis codes. The ICD-10-CM tree has at most 7 levels, depending on the branch. We did not look for clustering in Levels 1, 2, or 7, so as not to expend statistical power looking for clusters that were either too broad or too specific to be of clinical significance. We excluded some categories of diagnoses from consideration as not plausibly vaccine-related during the follow-up period. Details can be found in Yih et al. [7].

Included in analysis were incident diagnoses recorded in the inpatient or emergency department setting. "Incident" was defined as not preceded by another ICD-10 diagnosis code having the same first 3 characters (i.e., being in the same third level of the tree) in any setting (including outpatient) during the prior 400 days. We chose 400 days to enable ascertainment of pre-existing conditions that might have been recorded at a visit roughly 1 year prior, considering that some patients seek preventive care on an approximately annual basis.

We evaluated case clustering in all intervals between 2 and 28 days long that started on or after Day 1 after the booster. The comparison period to evaluate each eligible potential risk window consisted of the days within the follow-up period that were not in the risk window being evaluated. For example, when the potential risk window of Days 7–10 was being evaluated at a particular instant of the analysis, then Days 1–6 and Days 11–56 together were serving as the comparison period. Events on the day of the booster dose receipt (Day 0) were not included, as diagnoses

recorded on the same day as a vaccination may be for pre-existing conditions.

2.4. Statistical analysis

We used the self-controlled tree-temporal scan statistic, which is a hypothesis-free method that does not require pre-specifying either specific health outcomes of interest or any specific post-exposure period of putative increased risk. With the tree-temporal scan statistic, one intentionally considers many potential clusters of cases across two dimensions in combination:1) the hierarchical structure (tree) of diagnoses (ICD-10-CM codes, in this study) and 2) time, i.e., cases of each diagnosis group are checked for temporal clustering within the pre-defined post-exposure follow-up window. The method is described in greater detail in two recent reports [7,14].

We pre-specified the p-value cut-off for statistical significance for cluster identification as 0.01, preferring this to the more conventional 0.05 in order to guard against false signals across the numerous clusters being evaluated. In the tables of statistical results, we show all groupings with $p \leq 0.05$ for context, shading ones with $0.01 < p \leq 0.05$ in gray, but the term "cluster" is reserved for those that were statistically significant by our pre-specified criterion of $p \leq 0.01$.

The statistical analyses were conducted using TreeScan version 2.0 [15].

The study was approved by the Institutional Review Boards of all the VSD sites and was conducted in a manner consistent with federal law and CDC policy.

3. Results

Table 1 presents the number of recipients of each of the four booster types, with their distribution by demographic characteristics. The most frequent booster type was Pfizer-BioNTech after an mRNA primary series, with 2,467,865 doses. Next was Moderna after an mRNA primary series, with 1,873,849 doses. These were followed in frequency by an mRNA booster after Janssen (170,482 doses) and Janssen after Janssen (65,238 doses). The 40–64-year age group was the largest for all booster types, although the percentage comprised by this group varied across booster types. People aged ≥ 65 years made up a smaller proportion of recipients of boosters after Janssen compared with other booster types, partly reflecting the fact that only 13 % of Janssen primary vaccinees were aged ≥ 65 years [7]. Of vaccinees of known "race" (about three-quarters of the total), White people comprised the largest fraction, roughly half, for all 4 booster types, followed by Asian, Black/African American, Native Hawaiian/other Pacific Islander, and American Indian/Alaska Native. Females made up 56 % of post-mRNA mRNA booster recipients. The sex ratio of post-Janssen booster recipients was more even. Between 71 % and 77 % of first boosters captured were given in 2021.

3.1. Pfizer-BioNTech booster after mRNA primary series

Results of cluster detection to identify associations between vaccine and safety outcomes for the Pfizer-BioNTech booster after an mRNA primary series for all ages combined are shown in Table 2. We saw clusters of unspecified adverse effects or complications (T50 and T88) within the first 3 days after vaccination (p = 0.0001). Within the first 4 days after vaccination, there were also clusters of fever, myalgia, syncope, enlarged lymph nodes, malaise and fatigue, and 'pain in throat and chest' (p = 0.0001). We also saw clusters of COVID-19 disease (U07.1 and J12.82) within the first 10 days after vaccination (p = 0.0001). Another notable observation, although not statistically significant (p = 0.0163), was the grouping of 8 acute myocarditis cases in Days 3–4 after vaccination.

Nothing novel emerged in the age-stratified analyses, that is, all clusters detected in those analyses concerned outcomes of which clusters were found in the all-ages analysis.

3.2. Moderna booster after mRNA primary series

Table 3 shows the results for the Moderna booster after an mRNA primary series for all ages combined. We saw clusters of unspecified adverse effects (T50 and T88) (p = 0.0001), as well as of fever, myalgia, syncope, malaise and fatigue, headache (all with p = 0.0001), and pain (p = 0.0009), all within the first few days after vaccination. There was a COVID-19 (U07.1) cluster on Days 2–9

Table 1
Distribution of first-booster recipients by type of booster and demographic characteristics.

	Pfizer-BioNTech after 2 mRNA		Moderna after 2 mRNA		mRNA after Janssen		Janssen after Janssen	
Number of vaccinees	2,467,865		1,873,849		170,482		65,238	
Age								
<18*	189,906	8 %	–	–	–	–	–	–
18–39	609,888	25 %	430,254	23 %	51,737	30 %	12,871	20 %
40–64	992,110	40 %	806,731	43 %	97,011	57 %	38,920	60 %
65+	675,961	27 %	636,864	34 %	21,734	13 %	13,447	21 %
Ethnicity								
Non-Hispanic	1,936,904	78 %	1,467,680	78 %	137,721	81 %	49,517	76 %
Hispanic	530,961	22 %	406,169	22 %	32,761	19 %	15,721	24 %
Race								
Unknown	661,586	27 %	489,304	26 %	44,427	26 %	18,965	29 %
American Indian/Alaska Native	8,028	0 %	6,668	0 %	642	0 %	266	0 %
Asian	449,270	18 %	300,920	16 %	27,672	16 %	8,304	13 %
Black or African American	138,842	6 %	110,588	6 %	10,217	6 %	6,403	10 %
Native Hawaiian/other Pacific Islander	16,869	1 %	11,694	1 %	966	1 %	468	1 %
White	1,193,270	48 %	954,675	51 %	86,558	51 %	30,832	47 %
Sex								
Female	1,387,375	56 %	1,045,280	56 %	86,111	51 %	31,747	49 %
Male	1,080,251	44 %	828,425	44 %	84,347	49 %	33,484	51 %
Other/unknown	239	0 %	144	0 %	24	0 %	7	0 %

* 99.9 % of those in the < 18 category were aged 12–17 years.

Table 2
Clusters and less statistically significant groupings of adverse event cases found in the 56 days after the Pfizer-BioNTech COVID-19 vaccine booster dose following an mRNA primary series, all ages combined.* (All clusters or groupings with $p \leq 0.05$ are shown, but rows for groupings with $0.01 < p \leq 0.05$ are in italics.).

ICD-10 code	Adverse Event	Total Number of Cases	Risk Window Start Day	Risk Window End Day	Number of Cases in Risk Window	Attribu-table Risk per 100,000 Doses	Log Likeli-hood Ratio Test Statistic	P-Value
T50	Poisoning by, adverse effect of and underdosing of diuretics and other and unspecified drugs, medicaments and biological substances	774	1	2	244	9.10	318.7	0.0001
T50.B95	Adverse effect of other viral vaccines	251	1	3	196	7.80	351.4	0.0001
T50.Z95	Adverse effect of other vaccines and biological substances	71	1	3	60	2.40	112.0	0.0001
T88	Other complications of surgical and medical care, not elsewhere classified	158	1	3	98	3.80	154.8	0.0001
T88.1	Other complications following immunization, not elsewhere classified	108	1	3	93	3.70	175.3	0.0001
R50	Fever of other and unknown origin	1354	1	2	140	3.90	58.7	0.0001
R50.9	Fever, unspecified	1195	1	2	117	3.20	44.9	0.0001
R50.8	*Other specified fever*	*153*	*1*	*2*	*21*	*0.66*	*13.0*	*0.0167*
R50.83	Postvaccination fever	18	1	2	17	0.69	39.6	0.0001
U07	Emergency use of U07	1592	2	10	398	7.70	45.5	0.0001
U07.1	COVID-19	1590	2	10	398	7.70	45.7	0.0001
M79	Other and unspecified soft tissue disorders, not elsewhere classified	2417	1	3	211	3.70	25.6	0.0001
M79.1	Myalgia	390	1	3	69	2.10	36.7	0.0001
M79.10	Myalgia, unspecified site	305	1	3	63	2.00	40.6	0.0001
R55	Syncope and collapse	2587	1	2	185	4.00	37.4	0.0001
R59	Enlarged lymph nodes	376	2	4	65	2.00	36.5	0.0001
R59.0	Localized enlarged lymph nodes	248	2	4	40	1.20	20.5	0.0001
R59.1	Generalized enlarged lymph nodes	85	1	4	25	0.84	17.9	0.0001
R53	Malaise and fatigue	2494	1	2	170	3.50	30.3	0.0001
R53.8	Other malaise and fatigue	873	1	2	68	1.60	16.8	0.0002
R53.83	*Other fatigue*	*583*	*1*	*2*	*47*	*1.10*	*12.5*	*0.0279*
R53.1	Weakness	1608	1	4	171	2.80	16.3	0.0004
R07	Pain in throat and chest	7262	1	4	633	6.50	21.5	0.0001
R07.9	*Chest pain, unspecified*	*4227*	*1*	*13*	*1084*	*8.30*	*13.1*	*0.0155*
J12.8	Other viral pneumonia	272	4	10	69	1.70	16.4	0.0004
J12.82	Pneumonia due to coronavirus disease 2019	259	4	10	68	1.70	17.5	0.0001
I40	*Acute myocarditis*	*20*	*3*	*4*	*8*	*0.31*	*13.0*	*0.0163*
I87.30	*Chronic venous hypertension (idiopathic) without complications*	*20*	*30*	*31*	*8*	*0.31*	*12.2*	*0.0406*

* Codes sharing the same first three characters are nested together. These nests of codes are arranged in descending order of the largest test statistic in the nest.

after vaccination (p = 0.0001). In addition, there were clusters of urticaria, allergy, and rash within Days 10–15 after vaccination (p = 0.0001).

In the analyses of Moderna boosters in the groups aged 40–64 and ≥ 65 years, no outcomes emerged that were not also in the all-ages results. However, some new outcomes were seen for the group aged 18–39 years—there were clusters of 'pain in throat and chest' (p = 0.0001) and enlarged lymph nodes (p = 0.0083), both on Days 1–3 (Table 4).

3.3. mRNA booster after Janssen

For the mRNA booster after Janssen, the only cluster found in the all-ages analysis was for "adverse effect of other vaccines and biological substances" (T50.Z95) on Days 1–2 after vaccination (p = 0.0066). There were no clusters in the age-stratified analyses.

3.4. Janssen booster after Janssen

In the all-ages analysis of the Janssen booster after Janssen, no clusters were found. In the age-stratified analyses, there was one cluster, of viral pneumonia (J12) on Days 29–30 after vaccination in those aged ≥ 65 years (p = 0.0082); 7 of the 20 total cases were in this 2-day window.

4. Discussion

In these hypothesis-generating analyses of more than 2.4 million recipients of Pfizer BioNTech boosters and more than 1.8 million recipients of Moderna boosters after an mRNA primary series, the outcomes showing clustering were in large part a subset of those found in previous TreeScan analyses of the COVID-19 primary vaccine series [7]. These included unspecified adverse events, which in a previous study using the same method to investigate a different vaccine were found to represent mostly local injection site reactions and systemic conditions not uncommon after vaccination, e.g. fever and headache [16]). Other outcomes forming clusters in both the primary-series and boosters analyses were common vaccine-associated adverse events such as fever, myalgia, syncope, and malaise and fatigue. In addition, in the case of the mRNA boosters, clusters of COVID-19 were detected during the first 10 days after vaccination, before the boosters would have induced a boost in immunity.

A signal after the post-mRNA Moderna booster that was not seen in the primary series TreeScan analyses [7] was for urticaria/allergy/rash within Days 10–15. This delayed local reaction has been reported in the literature after a Moderna booster [17] as well as after Moderna Doses 1 and 2 (with the reaction after Dose 2 occurring sooner than after Dose 1) [18]. In their series of 12 cases after Dose 1, Blumenthal et al. report that symptoms resolved a median of 6 days after onset [18]. The fact that we detected delayed urticaria after the Moderna booster but not in

Table 3
Clusters and less statistically significant groupings of adverse event cases found in the 56 days after the Moderna booster following an mRNA primary series, all ages combined.* (All clusters or groupings with $p \leq 0.05$ are shown, but rows for groupings with $0.01 < p \leq 0.05$ are in italics.).

ICD-10 code	Adverse Event	Total Number of Cases	Risk Window Start Day	Risk Window End Day	Number of Cases in Risk Window	Attribu-table Risk per 100.000 Doses	Log Likeli-hood Ratio Test Statistic	P-Value
T50	Poisoning by, adverse effect of and underdosing of diuretics and other and unspecified drugs, medicaments and biological substances	613	1	2	191	9.30	239.7	0.0001
T50.B95	Adverse effect of other viral vaccines	210	1	3	160	8.40	275.4	0.0001
T50.Z95	Adverse effect of other vaccines and biological substances	61	1	4	56	3.00	92.8	0.0001
L50	Urticaria	519	11	15	283	14.00	270.7	0.0001
L50.9	Urticaria, unspecified	403	11	15	231	11.00	230.6	0.0001
L50.0	Allergic urticaria	101	10	15	57	2.80	48.2	0.0001
T78	Adverse effects, not elsewhere classified	519	11	15	182	7.90	110.6	0.0001
T78.4	Other and unspecified allergy	361	11	15	141	6.30	97.1	0.0001
T78.40	Allergy, unspecified	349	11	15	136	6.10	93.5	0.0001
T88	Other complications of surgical and medical care, not elsewhere classified	111	1	4	62	3.10	74.9	0.0001
T88.1	Other complications following immunization, not elsewhere classified	60	1	4	55	2.90	91.0	0.0001
R50	Fever of other and unknown origin	969	1	2	120	4.70	61.3	0.0001
R50.9	Fever, unspecified	833	1	2	98	3.70	46.6	0.0001
R50.8	*Other specified fever*	*132*	*1*	*2*	*20*	*0.84*	*13.2*	*0.0131*
R50.83	Postvaccination fever	19	1	2	15	0.79	31.7	0.0001
M79	Other and unspecified soft tissue disorders, not elsewhere classified	1917	1	2	128	3.20	18.8	0.0001
M79.1	Myalgia	331	1	2	60	2.60	47.9	0.0001
M79.10	Myalgia, unspecified site	254	1	2	55	2.50	51.8	0.0001
R55	Syncope and collapse	2085	1	2	176	5.50	46.9	0.0001
U07	Emergency use of U07	1417	2	9	296	6.80	28.4	0.0001
U07.1	COVID-19	1414	2	9	295	6.80	28.2	0.0001
R53	Malaise and fatigue	2095	1	2	150	4.00	27.0	0.0001
R53.8	Other malaise and fatigue	715	1	6	128	3.30	17.2	0.0001
R53.83	Other fatigue	484	1	6	90	2.40	13.6	0.0076
R53.1	Weakness	1375	1	3	124	2.80	14.0	0.0049
R21	Rash and other nonspecific skin eruption	355	12	14	57	2.10	22.7	0.0001
R51	Headache	2222	1	7	366	6.20	17.9	0.0001
R51.9	Headache, unspecified	2220	1	7	366	6.20	18.0	0.0001
R52	Pain, unspecified	178	1	2	25	1.00	15.0	0.0009
J12.82	*Pneumonia due to coronavirus disease 2019*	*235*	*2*	*9*	*62*	*1.90*	*12.4*	*0.0289*

* Codes sharing the same first three characters are nested together. These nests of codes are arranged in descending order of the largest test statistic in the nest.

the analyses of the Moderna primary series with its larger sample size suggests that the reaction may be stronger, inducing more patients to seek medical care for it, or that it occurs more frequently after the booster.

In the previous analysis of the primary series, clusters of COVID-19 (U07.1 and J12.82) and of presumed complications of SARS-CoV-2 infection were seen within the first 3 weeks after Dose 1 of the mRNA vaccines [7]. After mRNA boosters, there were clusters of COVID-19 within the first 10 days of the booster shot, before the booster would have reached maximum effectiveness; these clusters likely reflected suppression of (greater immunity to) COVID-19 disease later in follow-up. The rate of emergency department or inpatient visits with COVID-19 (U07.1) during the 56 days of follow-up after boosters was 6.4 per 10,000 Pfizer-BioNTech booster recipients and 7.5 per 10,000 Moderna booster recipients who had a prior mRNA COVID-19 vaccine primary series. Unlike in the first 3 weeks after Dose 1, there were no clusters of sepsis, respiratory failure, or hypoxemia, which had been deemed manifestations of COVID-19 disease. There are several possible reasons for the fewer presumed manifestations of COVID-19 observed after mRNA boosters than after Dose 1. Greater protection might have accumulated from exposure to the primary series and possibly to natural SARS-COV-2, the virus that causes COVID-19. The circulation of less virulent variants by the fall of 2021 may have also played a role. Finally, the booster analyses had somewhat lower statistical power due to smaller numbers of boosters.

Other clusters seen after Dose 1 or 2 of Pfizer-BioNTech that were not seen in follow-up after post-mRNA Pfizer-BioNTech boosters were: the common vaccine-associated adverse events of urticaria, nausea and vomiting, headache, chills, and allergy; palpitations and abnormalities of breathing; and myocarditis/pericarditis, although there was a grouping of acute myocarditis (I40) that was just under the threshold for statistical significance ($p = 0.0163$) (Table 2), seen also in the analysis of the < 18 year age group ($p = 0.0509$). Clusters seen after Dose 1 or 2 of Moderna not seen after post-mRNA Moderna boosters were: other serum reactions, nausea and vomiting, chills, 'pain in throat and chest', and tachycardia. The absence of such clusters after mRNA boosters may have been due to less reactogenicity (considering that many of the primary series clusters appeared to be after Dose 2, which was typically received only 3 or 4 weeks after Dose 1) and/or to less statistical power (considering the smaller numbers of booster doses than first doses in our analyses). It is also possible that those receiving boosters were different from (e.g., healthier than) those receiving the primary series.

Regarding myocarditis/pericarditis, in the primary series, there were clusters detected within Days 23–26 after Pfizer-BioNTech Dose 1 vaccination (very likely in the week after Dose 2) in the all-ages analysis as well as for the 12–17 year and 18–39-year age groups. No clusters of myocarditis/pericarditis were seen among the Moderna primary series vaccinees, although non-statistically significant groupings of this outcome were present in

Table 4
Clusters and less statistically significant groupings of adverse event cases found in the 56 days after the Moderna booster following an mRNA primary series, 18–39 year old age group.* (All clusters or groupings with $p \leq 0.05$ are shown, but rows for groupings with $0.01 < p \leq 0.05$ are in italics.).

ICD-10 code	Adverse Event	Total Number of Cases	Risk Window Start Day	Risk Window End Day	Number of Cases in Risk Window	Attribu-table Risk per 100,000 Doses	Log Likeli-hood Ratio Test Statistic	P-Value
L50	Urticaria	284	10	15	202	44.00	181.2	0.0001
L50.9	Urticaria, unspecified	223	11	15	153	34.00	149.9	0.0001
L50.0	Allergic urticaria	53	10	15	36	7.80	30.8	0.0001
T78	Adverse effects, not elsewhere classified	223	10	15	121	25.00	82.4	0.0001
T78.4	Other and unspecified allergy	182	10	15	104	22.00	74.9	0.0001
T78.40	Allergy, unspecified	177	10	15	103	21.00	75.7	0.0001
T50	Poisoning by, adverse effect of and underdosing of diuretics and other and unspecified drugs, medicaments and biological substances	86	1	3	51	11.00	71.4	0.0001
T50.B95	Adverse effect of other viral vaccines	46	1	3	39	9.00	67.4	0.0001
T50.Z95	Adverse effect of other vaccines and biological substances	13	1	4	13	3.00	21.7	0.0001
R21	Rash and other nonspecific skin eruption	123	12	15	40	7.30	21.8	0.0001
T88	Other complications of surgical and medical care, not elsewhere classified	15	1	2	10	2.30	18.7	0.0001
T88.1	Other complications following immunization, not elsewhere classified	11	1	2	9	2.10	18.5	0.0001
R07	Pain in throat and chest	807	1	3	95	12.00	17.9	0.0001
R07.8	Other chest pain	390	1	3	51	6.90	12.4	0.0047
R07.89	*Other chest pain*	*350*	*1*	*4*	*54*	*7.00*	*11.4*	*0.0167*
M79.1	Myalgia	77	1	2	18	3.60	16.7	0.0001
M79.10	Myalgia, unspecified site	68	1	2	17	3.50	16.8	0.0001
R50	Fever of other and unknown origin	141	1	2	22	4.00	13.5	0.001
R50.9	Fever, unspecified	127	1	2	20	3.60	12.4	0.005
R59	Enlarged lymph nodes	38	1	3	13	2.70	12.0	0.0083
R59.1	*Generalized enlarged lymph nodes*	*18*	*1*	*4*	*10*	*2.20*	*11.4*	*0.0156*
R55	*Syncope and collapse*	*211*	*1*	*2*	*26*	*4.20*	*11.6*	*0.0131*
L29	*Pruritus*	*38*	*11*	*15*	*17*	*3.30*	*10.8*	*0.0338*
L29.9	*Pruritus, unspecified*	*36*	*11*	*15*	*17*	*3.40*	*11.5*	*0.0139*
R09.89	*Other specified symptoms and signs involving the circulatory and respiratory systems*	*23*	*26*	*27*	*8*	*1.70*	*11.2*	*0.0212*
R52	*Pain, unspecified*	*21*	*1*	*2*	*8*	*1.70*	*10.8*	*0.0341*

* Codes sharing the same first three characters are nested together. These nests of codes are arranged in descending order of the largest test statistic in the nest.

Days 31–32 in the all-ages and 18–39-year groups [7]. In VSD's real-time sequential analysis of booster safety using pre-specified outcomes, a signal appeared for myocarditis/pericarditis after Pfizer-BioNTech or Moderna boosters; rate ratios for chart-confirmed myocarditis/pericarditis 0–7 days after both Pfizer-BioNTech and Moderna boosters in the 12–39 year age group were elevated but not more (and possibly less) than after the second dose of the primary series [19]. The fact that we did not detect a statistically significant signal for myocarditis or pericarditis after either Pfizer-BioNTech or Moderna boosters was likely due in part to the smaller sample size of boosters compared with the primary series in our analyses and in part to the fact that scanning tens of thousands of diagnoses and hundreds of time intervals uses statistical power, such that not all rare health outcomes producing a signal in a more targeted study would necessarily signal in a data-mining study like ours, even with a similar number of vaccinees.

Very few potential adverse events were detected after post-Janssen boosters, whether the booster was an mRNA dose (n = 170,482) or another Janssen dose (n = 65,238). The much smaller numbers of post-Janssen boosters made for lower statistical power than what was available for the mRNA boosters after an mRNA primary series. The cluster of viral pneumonia (J12) on Days 29–30 after post-Janssen Janssen boosting of those aged ≥ 65 years ($p = 0.0082$) may have been simply due to chance. Considering that viral pneumonia is not a biologically plausible safety concern for this non-replicating viral vector vaccine, we did not think it merited investigation.

In summary, in untargeted data-mining surveillance for possible adverse events after first mRNA COVID-19 booster administration, we did not identify any new safety concerns. The safety profile of post-mRNA mRNA boosters was similar to what we found after the primary series except for delayed-onset urticaria/allergy/rash after the Moderna booster. Although this outcome has been reported in the literature after first, second, and booster doses of Moderna, we did not find clusters of it after the Moderna primary series [7], and it may be that the outcome is more pronounced or occurs more frequently after the booster. The number of people receiving a booster after a Janssen primary vaccination was too low to assess the safety of post-Janssen boosters, a situation likely to persist given the ACIP's preferential recommendation for use of the mRNA vaccines over the Janssen vaccine in December 2021 [13].

Data availability

Researchers may request the data via the standard VSD data sharing program described on CDC's public website: https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/accessing-data.html.

Declaration of Competing Interest

WK Yih has received research funding from Pfizer in the past. JC Nelson received grant funding to participate on the External Safety Advisory Board for Moderna's COVID-19 vaccine program in 2020 – April 2021. L Qian has received funding from Moderna, GlaxoSmithKline, and Dynavax for work unrelated to this manuscript. The other authors report no conflicts.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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