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# Surveillance for Adverse Events After COVID-19 mRNA Vaccination

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**IMPORTANCE** Safety surveillance of vaccines against COVID-19 is critical to ensure safety, maintain trust, and inform policy.

**OBJECTIVES** To monitor 23 serious outcomes weekly, using comprehensive health records on a diverse population.

**DESIGN, SETTING, AND PARTICIPANTS** This study represents an interim analysis of safety surveillance data from Vaccine Safety Datalink. The 10 162 227 vaccine-eligible members of 8 participating US health plans were monitored with administrative data updated weekly and supplemented with medical record review for selected outcomes from December 14, 2020, through June 26, 2021.

**EXPOSURES** Receipt of BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) COVID-19 vaccination, with a risk interval of 21 days for individuals after vaccine dose 1 or 2 compared with an interval of 22 to 42 days for similar individuals after vaccine dose 1 or 2.

**MAIN OUTCOMES AND MEASURES** Incidence of serious outcomes, including acute myocardial infarction, Bell palsy, cerebral venous sinus thrombosis, Guillain-Barré syndrome, myocarditis/pericarditis, pulmonary embolism, stroke, and thrombosis with thrombocytopenia syndrome. Incidence of events that occurred among vaccine recipients 1 to 21 days after either dose 1 or 2 of a messenger RNA (mRNA) vaccine was compared with that of vaccinated concurrent comparators who, on the same calendar day, had received their most recent dose 22 to 42 days earlier. Rate ratios (RRs) were estimated by Poisson regression, adjusted for age, sex, race and ethnicity, health plan, and calendar day. For a signal, a 1-sided $P < .0048$ was required to keep type I error below .05 during 2 years of weekly analyses. For 4 additional outcomes, including anaphylaxis, only descriptive analyses were conducted.

**RESULTS** A total of 11 845 128 doses of mRNA vaccines (57% BNT162b2; 6 175 813 first doses and 5 669 315 second doses) were administered to 6.2 million individuals (mean age, 49 years; 54% female individuals). The incidence of events per 1 000 000 person-years during the risk vs comparison intervals for ischemic stroke was 1612 vs 1781 (RR, 0.97; 95% CI, 0.87-1.08); for appendicitis, 1179 vs 1345 (RR, 0.82; 95% CI, 0.73-0.93); and for acute myocardial infarction, 935 vs 1030 (RR, 1.02; 95% CI, 0.89-1.18). No vaccine-outcome association met the prespecified requirement for a signal. Incidence of confirmed anaphylaxis was 4.8 (95% CI, 3.2-6.9) per million doses of BNT162b2 and 5.1 (95% CI, 3.3-7.6) per million doses of mRNA-1273.

**CONCLUSIONS AND RELEVANCE** In interim analyses of surveillance of mRNA COVID-19 vaccines, incidence of selected serious outcomes was not significantly higher 1 to 21 days postvaccination compared with 22 to 42 days postvaccination. While CIs were wide for many outcomes, surveillance is ongoing.

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Safe and effective vaccines against SARS-CoV-2 are critical to ending the pandemic. Two messenger RNA (mRNA) vaccines (BNT162b2, Pfizer-BioNTech; and mRNA-1273, Moderna) were the first SARS-CoV-2 vaccines authorized in the US.[1,2] Large phase 3 trials for BNT162b2 and mRNA-1273 demonstrated that both vaccines were more than 94% effective against symptomatic SARS-CoV-2 infection.[3,4] Neither trial reported serious safety findings, and both observed low incidence of serious adverse events.

The BNT162b2 vaccine received an Emergency Use Authorization on December 11, 2020[1]; mRNA-1273, on December 18, 2020.[2] Vaccinations began in mid-December.[5]

Rare or serious outcomes associated with a vaccine may not be identified in phase 3 trials because of limited sample size, restrictive inclusion criteria, limited duration of follow-up, and trial participants who may differ from the population ultimately receiving the vaccine. Furthermore, there is limited experience with mRNA platforms.[6] Surveillance is critical to ensure safety, maintain trust, and inform policy.

Since 2006, the Vaccine Safety Datalink,[7] a collaboration between US health plans and the Centers for Disease Control and Prevention (CDC), has conducted weekly vaccine surveillance known as rapid cycle analysis.[8-11] When the first COVID-19 vaccine was administered in December 2020, weekly monitoring started immediately. This report includes interim findings on risk of adverse events after receipt of mRNA COVID-19 vaccines through June 2021.

### Key Points

**Question** Are mRNA COVID-19 vaccines associated with increased risk for serious health outcomes during days 1 to 21 after vaccination?

**Findings** In this interim analysis of surveillance data from 6.2 million persons who received 11.8 million doses of an mRNA vaccine, event rates for 23 serious health outcomes were not significantly higher for individuals 1 to 21 days after vaccination compared with similar individuals at 22 to 42 days after vaccination.

**Meaning** This analysis found no significant associations between vaccination with mRNA COVID-19 vaccines and selected serious health outcomes 1 to 21 days after vaccination, although CIs were wide for some rate ratio estimates and additional follow-up is ongoing.

## Methods

This study was approved by the institutional review boards of all participating health plan sites, with a waiver of informed consent, and was conducted consistent with federal law and CDC policy.

### Setting and Study Population

The population covered by the 8 data-contributing health plans comprises 12 506 658 people, representing 3.6% of the US population, and includes all ages, with approximately 16% aged 65 years or older and 20% younger than 18 years. Participating sites (Kaiser Permanente: Colorado, Northern California, Northwest, Southern California, and Washington; Marshfield Clinic; HealthPartners; and Denver Health) have comprehensive medical records for their members.

Participating sites routinely create dynamic files that are updated weekly and contain information on demographics (including race and ethnicity in fixed categories based on self-reported data from the participating health plans), immunizations, and diagnosis codes associated with all outpatient, emergency, and hospital encounters. Sites included race and ethnicity to identify disparities regarding vaccination rates.[12,13] In response to the pandemic, we created additional weekly files, including COVID-19 diagnoses and laboratory results. Surveillance included the 10 162 227 members of participating health plans aged 12 years or older.

Vaccination date, manufacturer, and dose number for each COVID-19 vaccine were recorded at the participating sites for the doses they delivered. All sites also capture COVID-19 vaccines administered outside of their health care system, including those administered in nursing homes, retail pharmacies, and government-run vaccination clinics; self-reported vaccinations; and those recorded in state immunization registries. This report includes only mRNA vaccines.

### Study Design

Each week since December 14, 2020, when vaccinations against COVID-19 began, we updated and analyzed all vaccinations and outcomes in the surveillance population. We analyzed the accumulating data to regularly update the Advisory Committee on Immunization Practices and address emerging vaccine safety concerns that arose elsewhere. The primary analyses compared outcome rates during risk intervals for individuals recently vaccinated with rates during comparison intervals for those less recently vaccinated. The surveillance protocol, including planned analyses not presented here, is available at https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/emergencypreparedness/index.html.

Our COVID-19 vaccine surveillance is anticipated to continue for a minimum of 2 years. This interim report includes mRNA vaccinations and outcome events from December 14, 2020, through June 26, 2021.

### Outcomes

We targeted 23 serious outcomes after consultation with CDC and study investigators in coordination with partners from the Food and Drug Administration, Department of Defense, and Department of Veterans Affairs (**Table 1**). We selected outcomes based on (1) inclusion in prior vaccine safety studies (acute disseminated encephalomyelitis, anaphylaxis, encephalitis/myelitis, Guillain-Barré syndrome, immune thrombocytopenia, Kawasaki disease, narcolepsy, seizures, and transverse myelitis); (2) imbalances in phase 3 COVID-19 vaccine clinical trials (appendicitis, Bell palsy); (3) hypothetical concerns regarding an association with COVID-19 disease (acute myocardial infarction, acute respiratory distress syndrome, disseminated intravascular

Table 1. Outcomes for Rapid Cycle Analysis of COVID-19 mRNA Vaccines

| Outcomes | Risk interval, d | Setting | Exclude if COVID-19 positive in the interval before vaccination, d[a] |
|---|---|---|---|
| Comparative analyses | 1-21 | | |
| Acute disseminated encephalomyelitis | | Emergency department, inpatient | NA |
| Acute myocardial infarction | | Emergency department, inpatient | 30 |
| Appendicitis | | Emergency department, inpatient | NA |
| Bell palsy | | Emergency department, inpatient, outpatient | 30 |
| Cerebral venous sinus thrombosis | | Emergency department, inpatient | 30 |
| Convulsions/seizures | | Emergency department, inpatient | 30 |
| Disseminated intravascular coagulation | | Emergency department, inpatient | 42 |
| Encephalitis/myelitis/encephalomyelitis | | Emergency department, inpatient | 30 |
| Guillain-Barré syndrome | | Emergency department, inpatient | NA |
| Immune thrombocytopenia | | Emergency department, inpatient, outpatient | 30 |
| Kawasaki disease | | Emergency department, inpatient | NA |
| Myocarditis/pericarditis | | Emergency department, inpatient | 30 |
| Pulmonary embolism | | Emergency department, inpatient | 30 |
| Stroke | | | |
| Hemorrhagic | | Emergency department, inpatient | 30 |
| Ischemic | | Emergency department, inpatient | 30 |
| Thrombosis with thrombocytopenia syndrome[b] | | Emergency department, inpatient | 30 |
| Thrombotic thrombocytopenic purpura | | Emergency department, inpatient | 30 |
| Transverse myelitis | | Emergency department, inpatient | NA |
| Venous thromboembolism | | Emergency department, inpatient, outpatient | 30 |
| Descriptive monitoring only | Monitoring period, d | | |
| Acute respiratory distress syndrome | 0-84 | Emergency department, inpatient | 42 |
| Anaphylaxis | 0-1 | Emergency department, inpatient | NA |
| Multisystem inflammatory syndrome in children/adults | 0-84 | Emergency department, inpatient | NA |
| Narcolepsy/cataplexy | 0-84 | Emergency department, inpatient, outpatient | NA |

Abbreviation: NA, not applicable.

[a] Exclusion was applied to the entire population under surveillance. The rationale for excluding selected outcome events owing to recent COVID-19 infection was based on COVID-19 literature and subject matter expertise of outcomes known to be associated with COVID-19 infection. Timing of the exclusion period (30 or 42 days) was based on input from subject matter experts.

[b] Outcome included cerebral venous sinus thrombosis, splanchnic vein thrombosis, and arterial thrombosis.

coagulation, multisystem inflammatory syndrome in children and adults, myocarditis/pericarditis, pulmonary embolism, stroke [hemorrhagic and ischemic], thrombotic thrombocytopenic purpura, and venous thromboembolism); or (4) emerging concerns that have arisen during the course of surveillance (cerebral venous sinus thrombosis,[14] thrombosis with thrombocytopenia syndrome,[15] and a younger subgroup of the myocarditis/pericarditis outcome[16]). We limited most outcomes to the emergency department and inpatient settings; however, we included immune thrombocytopenia, Bell palsy, narcolepsy, and venous thromboembolism diagnosed in the outpatient setting (Table 1). We used *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* codes to identify outcomes and developed algorithms to ascertain incident cases based on prior studies, published literature, or expert opinion (eTables 1 and 2 in the Supplement). Where available, we also used an internal diagnostic code, "anaphylaxis due to COVID-19 vaccine" (all settings, including outpatient), to supplement case identification; these patients were required to have also sought care in the emergency department or inpatient setting on days 0 to 1. Clinical subject matter experts consulted on case ascertainment criteria for all outcomes.

## Medical Record Reviews

Surveillance activities included medical record reviews as needed to investigate potential signals or emerging concerns.

We prespecified that within 84 days after vaccination, all cases of Guillain-Barré syndrome, acute disseminated encephalomyelitis, transverse myelitis, cerebral venous sinus thrombosis, and myocarditis/pericarditis (among individuals aged 12-39 years) were to be reviewed and included in analyses only if confirmed. Medical record reviews were designed to ascertain both the diagnosis and the time of onset. We used the onset dates from these medical record reviews for the primary analysis.

All potential cases of anaphylaxis in vaccinated individuals during days 0 to 1 after vaccination also underwent a limited medical record review soon after identification to confirm diagnosis and exclude those with exposure to other known triggers (eg, peanut). This was followed by complete review 30 days later to include records from subsequent allergy and external health care encounters and adjudicated with the Brighton Collaboration criteria.[17] Brighton criteria require sudden onset after vaccination, rapid progression of signs and symptoms, involvement of 2 or more organ systems, and no clear alternative etiology for anaphylaxis. To allow 30 days for a complete review, we included cases identified through May 29, 2021.

## Statistical Analysis

We compared outcome incidence during a risk interval of days 1 to 21 after vaccination with outcome incidence in vaccinated concurrent comparators (eFigure 1 in the Supplement). These comparators were vaccinees who were concurrently—on the same calendar day—in a comparison interval that was 22 to 42 days after their most recent COVID-19 vaccination. For example, on March 1 individuals who were in their risk interval (eg, vaccinated from February 8-28) were compared with vaccinees who on March 1 had had their most recent dose 22 to 42 days earlier (eg, vaccinated January 18 to February 7). Vaccinees contributed to the primary analyses as exposed when in a 21-day risk interval after dose 1 or 2; they contributed as unexposed when in the comparison interval 22 to 42 days after their most recent dose. A similar comparison interval has been used in other vaccine safety studies.[18] This interval is valuable to prioritize timely detection of an early elevated risk; a substantial delay before comparator follow-up was observable would delay timely detection. In addition, a longer delay postvaccination could increase the potential for bias arising from unmeasured factors associated with receiving vaccination earlier vs later.

To reduce the possibility of confounding by demographic factors and factors associated with calendar time, we conducted analyses within strata defined by 5-year age group, sex, 8 race and ethnicity groups (those missing race or ethnicity were categorized as unknown), site, and calendar day. Race and ethnicity was used to adjust for confounding that may have arisen if the factor was associated with vaccination dates and outcome events.

We used Poisson regression to estimate an adjusted rate ratio (RR) and corresponding 95% CI, estimating the incidence in the risk interval compared with incidence in the comparison interval, averaged over the strata and calendar days. We reported nominal 95% CIs rather than CIs widened to correspond with the sequential tests that are described later because nominal CIs are more interpretable in this surveillance. The study protocol specified that nominal CIs continue to be updated and reported regardless of whether any sequential test yielded a signal.

Each Poisson regression model was fitted to aggregated count data: on each calendar day in each age-sex-race-site stratum, we counted the numbers of vaccinees and outcomes in the risk and comparison intervals. The dependent variable was the number of outcomes in the interval, the primary independent variable was whether the interval was a risk interval vs a comparison interval, and the offset term was the natural logarithm of the number of vaccinees in the interval. A stratum was informative only on a day when there was at least 1 person in the risk interval, at least 1 person in the comparison interval, and at least 1 outcome in either the risk interval or the comparison interval.

To estimate excess risk per million doses, we divided the risk interval's crude incidence rate by the adjusted RR, and then subtracted the result from the risk interval's crude incidence rate.

In this report, we feature analyses that combine follow-up after receipt of the BNT162b2 and mRNA-1273 vaccines and combine follow-up in the 21-day risk interval after dose 1 with follow-up in the 21-day risk interval after dose 2. Separate analyses were also conducted for each vaccine type and dose.

We conducted supplemental analyses to address emerging concerns about myocarditis/pericarditis, which included shorter risk intervals and examined temporal clustering of outcome events after vaccination, using the Kulldorff scan statistic.[19]

We also conducted supplemental analyses with unvaccinated concurrent comparators, using methods similar to those of the analyses with vaccinated concurrent comparators (eFigure 1 in the Supplement). For each calendar day, we compared the vaccinees in each age-sex-race-site stratum who were in the risk interval with all individuals in the same age-sex-race-site stratum who were unvaccinated on that calendar day. Analyses with unvaccinated comparators were considered supplemental—whereas vaccinated comparators were primary—under the assumption that vaccinees in the risk interval tended to be more similar to those in the comparison interval than to unvaccinated individuals (some of whom are unlikely ever to be vaccinated).

Supplemental analyses were intended to provide context for interpreting primary analyses and emerging concerns; they did not have a prespecified threshold for a statistical signal.

## Sequential Testing

Sequential tests were conducted weekly. For all outcomes except anaphylaxis, acute respiratory distress syndrome, multisystem inflammatory syndrome, and narcolepsy (discussed later), we conducted 1-sided sequential tests of the null hypothesis that the vaccine did not affect risk during the risk interval. The threshold for a signal was 1-sided $P < .0048$ to keep the overall chance of making a type I error below .05 during 2 years of weekly analyses (according to a Pocock-style alpha-spending plan,[20] designed by simulation). A signal would end formal sequential testing but would not end surveillance activities for that outcome. Rather, surveillance would continue to help interpret the signal. The sequential test threshold was designed to account for the number of weekly tests of the same hypothesis, but not for the multiplicity of hypotheses across different outcomes. The multiplicity of different hypotheses

Table 2. Vaccine Doses Administered to the Surveillance Population, December 14, 2020-June 26, 2021

| | BNT162b2 (N) | | mRNA-1273 (N) | | Both mRNA vaccines (N) | | | Surveillance population ≥12 y, No.[a] |
|---|---|---|---|---|---|---|---|---|
| | Dose 1 | Dose 2 | Dose 1 | Dose 2 | Dose 1 | Dose 2 | Total doses | |
| Total | 3 539 611 | 3 214 737 | 2 636 202 | 2 454 578 | 6 175 813 | 5 669 315 | 11 845 128 | 10 162 227 |
| Sex | | | | | | | | |
| Female | 1 909 585 | 1 738 663 | 1 435 437 | 1 341 000 | 3 345 022 | 3 079 663 | 6 424 685 | 5 326 063 |
| Male | 1 630 026 | 1 476 074 | 1 200 765 | 1 113 578 | 2 830 791 | 2 589 652 | 5 420 443 | 4 836 164 |
| Age group, y | | | | | | | | |
| 12-15 | 213 814 | 152 494 | 0 | 0 | 213 814 | 152 494 | 366 308 | 558 130 |
| 16-17 | 139 660 | 120 488 | 0 | 0 | 139 660 | 120 488 | 260 148 | 280 784 |
| 18-49 | 1 624 340 | 1 468 324 | 1 171 064 | 1 065 998 | 2 795 404 | 2 534 322 | 5 329 726 | 5 124 940 |
| 50-64 | 816 597 | 760 201 | 719 892 | 676 251 | 1 536 489 | 1 436 452 | 2 972 941 | 2 329 719 |
| 65-74 | 438 496 | 417 945 | 450 819 | 429 666 | 889 315 | 847 611 | 1 736 926 | 1 139 752 |
| ≥75 | 306 704 | 295 285 | 293 929 | 282 290 | 600 633 | 577 575 | 1 178 208 | 728 902 |
| Race and ethnicity | | | | | | | | |
| American Indian/ Alaska Native | 10 296 | 9295 | 8349 | 7675 | 18 645 | 16 970 | 35 615 | 31 430 |
| Asian | 576 803 | 528 677 | 364 432 | 343 035 | 941 235 | 871 712 | 1 812 947 | 1 234 172 |
| Black, non-Hispanic | 184 621 | 163 717 | 150 120 | 137 608 | 334 741 | 301 325 | 636 066 | 668 516 |
| Hispanic/Latino | 767 978 | 679 008 | 616 513 | 567 361 | 1 384 491 | 1 246 369 | 2 630 860 | 2 509 139 |
| Native Hawaiian/ Pacific Islander | 22 858 | 20 562 | 16 053 | 14 856 | 38 911 | 35 418 | 74 329 | 61 880 |
| White, non-Hispanic | 1 477 545 | 1 368 800 | 1 148 149 | 1 080 562 | 2 625 694 | 2 449 362 | 5 075 056 | 4 130 350 |
| Multiple/other[b] | 123 770 | 111 871 | 88 600 | 82 433 | 212 370 | 194 304 | 406 674 | 338 984 |
| Unknown | 375 740 | 332 807 | 243 986 | 221 048 | 619 726 | 553 855 | 1 173 581 | 1 187 756 |

[a] Total enrolled population that has Emergency Use Authorization for existing COVID-19 vaccines. All enrolled persons aged 12 years or older are included in the weekly COVID-19 vaccine surveillance.

[b] Includes persons with more than 1 non-Hispanic race and ethnicity and all other non-Hispanic races and ethnicities.

tested would be considered informally in the context of investigating signals. If there were a signal, it would be interpreted as exploratory insofar as the large number of hypotheses tested increases the possibility of a false-positive signal.

### Descriptive Monitoring (No Comparators, RR Estimates, or Hypothesis Tests)

We conducted only descriptive monitoring for anaphylaxis, acute respiratory distress syndrome, multisystem inflammatory syndrome, and narcolepsy (ie, no RR estimates or hypothesis tests), given the lack of appropriate comparators. For these outcomes, we tabulated all observed cases that occurred within 84 days postvaccination.

For anaphylaxis, we also estimated the rate of confirmed anaphylaxis per million doses.

We used SAS version 9.4 (SAS Institute) for all analyses.

## Results

From December 14, 2020, through June 26, 2021, 11 845 128 total doses of mRNA vaccines were administered to 6.2 million individuals (mean age, 49 years; 54% female). Of these, 6 754 348 were BNT162b2 and 5 090 780 were mRNA-1273 vaccines. There were 6 175 813 first doses and 5 669 315 second doses (**Table 2**). Overall, vaccinees aged 18 to 49 years received the largest number of doses (5 124 940); however, vaccination coverage was highest among members aged 75 years or older (82.4% with 1 dose; 79.2% with 2). Coverage was also higher among White and Asian persons compared with other racial and ethnic groups, including among the 11.7% of the surveillance population categorized as unknown race.

The number of outcome events during the 21-day risk interval ranged from 0 for Kawasaki disease to 1059 (1612 per 1 000 000 person-years) for ischemic stroke (**Table 3**). In weekly analyses, none of the outcomes met the signaling criteria of 1-sided $P < .0048$ (Table 3). In analyses through June 26, 2021, the incidence per 1 000 000 person-years during the risk and comparison intervals and adjusted RR ranged from 45 vs 69 (RR, 0.70; 95% CI, 0.39-1.28) for disseminated intravascular coagulation to 9 vs 6 (RR, 2.60; 95% CI, 0.47-20.66) for thrombotic thrombocytopenic purpura. For the most frequent outcomes, the incidence per 1 000 000 person-years during the risk vs comparison intervals and adjusted RR for ischemic stroke were 1612 vs 1781 (RR, 0.97; 95% CI, 0.87-1.08); for appendicitis, 1179 vs 1345 (RR, 0.82; 95% CI, 0.73-0.93); for acute myocardial infarction, 935 vs 1030 (RR, 1.02; 95% CI, 0.89-1.18); for venous thromboembolism, 952 vs 896 (RR, 1.16; 95% CI, 1.00-1.34); and for Bell palsy, 822 vs 825 (RR, 1.00; 95% CI, 0.86-1.17). The highest estimates of excess cases per million doses were 7.5 (95% CI, -0.1 to 14.0) for venous thromboembolism and 1.2 (95% CI, -6.9 to 8.3) for acute myocardial infarction (Table 3).

None of the 10 cerebral venous sinus thrombosis cases were associated with thrombocytopenia.

Table 3. Outcome Events in the 21-Day Risk Interval After Either Vaccine Dose Compared, on the Same Calendar Day, With Outcome Events in Individuals 22-42 Days After Their Most Recent Dose, December 14, 2020-June 26, 2021

| Outcome | Events in risk interval (events/million person-years)[a] | Events in comparison interval (events/million person-years)[a,b] | Adjusted rate ratio[c] (95% CI)[d] | *P* value | | Signal, 1-sided *P* < .0048[e] | Excess cases in risk interval per million doses (95% CI)[f] |
|---|---|---|---|---|---|---|---|
| | | | | 2-Sided[d] | 1-Sided | | |
| Thrombotic thrombocytopenic purpura | 6 (9.1) | 2 (5.5) | 2.60 (0.47-20.66) | .29 | .23 | No | 0.3 (-0.6 to 0.5) |
| Cerebral venous sinus thrombosis[g] | 7 (10.6) | 3 (8.2) | 1.55 (0.37-8.17) | .59 | .41 | No | 0.2 (-1.1 to 0.5) |
| Transverse myelitis[g] | 2 (3.0) | 1 (2.7) | 1.45 (0.10-47.73) | .82 | .64 | No | 0.1 (-1.6 to 0.2) |
| Encephalitis/myelitis/ encephalomyelitis | 16 (25.7) | 5 (13.7) | 1.27 (0.45-4.10) | .69 | .44 | No | 0.3 (-1.8 to 1.1) |
| Myocarditis/pericarditis | 87 (131.7) | 39 (106.9) | 1.18 (0.79-1.79) | .44 | .25 | No | 1.2 (-2.1 to 3.3) |
| Venous thromboembolism | 626 (951.9) | 327 (895.9) | 1.16 (1.00-1.34) | .05 | .03 | No | 7.5 (-0.1 to 14.0) |
| Immune thrombocytopenia | 48 (72.6) | 23 (63.0) | 1.12 (0.65-1.97) | .70 | .40 | No | 0.4 (-2.2 to 2.1) |
| Convulsions/seizures | 285 (431.3) | 150 (411.0) | 1.04 (0.84-1.29) | .74 | .39 | No | 0.9 (-4.8 to 5.6) |
| Acute myocardial infarction | 613 (935.3) | 375 (1030.2) | 1.02 (0.89-1.18) | .75 | .39 | No | 1.2 (-6.9 to 8.3) |
| Pulmonary embolism | 503 (762.8) | 290 (794.6) | 1.01 (0.86-1.19) | .92 | .48 | No | 0.4 (-7.2 to 6.9) |
| Bell palsy | 535 (821.8) | 301 (824.7) | 1.00 (0.86-1.17) | .99 | .52 | No | 0.0 (-7.9 to 6.7) |
| Stroke, ischemic | 1059 (1611.8) | 650 (1780.9) | 0.97 (0.87-1.08) | .61 | .70 | No | -2.7 (-13.8 to 7.2) |
| Stroke, hemorrhagic | 240 (364.7) | 149 (408.2) | 0.90 (0.72-1.13) | .37 | .83 | No | -2.3 (-8.3 to 2.5) |
| Thrombosis with thrombocytopenia syndrome | 73 (112.0) | 53 (145) | 0.86 (0.58-1.27) | .45 | .81 | No | -1.0 (-4.6 to 1.4) |
| Appendicitis | 762 (1178.9) | 491 (1345.2) | 0.82 (0.73-0.93) | .002 | >.99 | No | -14.8 (-25.5 to -5.3) |
| Guillain-Barré syndrome[g] | 10 (15.1) | 6 (16.4) | 0.70 (0.22-2.31) | .53 | .83 | No | -0.4 (-3.0 to 0.5) |
| Disseminated intravascular coagulation | 30 (45.4) | 25 (68.5) | 0.70 (0.39-1.28) | .25 | .91 | No | -1.1 (-4.1 to 0.6) |
| Kawasaki disease | 0 | 2 (5.5) | 0.00 (0.00-2.52) | .16 | .16 | No | -0.3 (-0.3 to 0.0) |
| Acute disseminated encephalomyelitis[g] | 2 (3.0) | 0 | NE (0.07-NE) | .66 | .66 | No | 0.2 (-2.5 to NE) |

Abbreviation: NE, not estimable.

[a] There were 660 766 person-years of follow-up in the risk interval and 364 988 person-years in the comparison interval.

[b] Comparison interval was 22 to 42 days after either dose 1 or 2. The smaller case counts were due to the reduced available person-time of follow-up in the comparison interval. Most comparator follow-up was 22 to 42 days after dose 2 but some was 22 to 42 days after dose 1 in individuals who had not received dose 2.

[c] Overall estimate from Poisson regression stratified by site, 5-year age group, sex, race and ethnicity, and calendar date.

[d] CIs and *P* values do not account for the multiple chances for a false-positive signal during surveillance.

[e] One-sided *P* < .0048 required for a signal. This keeps the probability of a false-positive signal (owing to chance alone) below .05 in 2 years of surveillance.

[f] CIs for the excess risk estimates were based on the CIs of the corresponding adjusted rate ratios.

[g] Only medical record–confirmed cases are included in the analysis.

None of the dose 1, dose 2, and vaccine product analyses met the signaling criteria of a 1-sided *P* < .0048 (eTable 3 in the Supplement).

During days 0 to 21 postvaccination, there were a total of 34 cases of confirmed myocarditis/pericarditis among individuals aged 12 to 39 years, of whom 53% were aged 12 to 24 years, 85% were male, 82% were hospitalized (median length of stay, 1 day), and nearly all were recovered at record review (eTable 4 in the Supplement). Cases were significantly clustered within the 0 to 5 days after vaccination (*P* < .001) (eFigure 2 in the Supplement). In supplemental analyses using vaccinated concurrent comparators, incidence per 1 000 000 person-years during the risk vs comparison intervals and adjusted RR were 321 vs 35 (RR, 9.83; 95% CI, 3.35-35.77) during days 0 to 7 after vaccination, corresponding to 6.3 additional cases per million doses (95% CI, 4.9-6.8) (**Table 4**). After dose 2, RR estimates were higher for both BNT162b2 and mRNA-1273 vaccines (eTable 5 in the Supplement).

Supplemental analyses among all ages, using unvaccinated comparators, were mostly consistent with the primary vaccinated comparator analyses; however, for myocarditis/pericarditis, incidence per 1 000 000 person-years during the risk vs comparison intervals and adjusted RR were 132 vs 83 (RR, 1.39; 95% CI, 1.05-1.82) (eTable 6 in the Supplement).

## Descriptive Monitoring

There were 183 potential anaphylaxis cases during days 0 to 1 after vaccination; 171 (93%) underwent full review and 55 (32%) were confirmed and adjudicated at Brighton level 1 to 3 (**Table 5**). Nearly all confirmed anaphylaxis cases were in female individuals (95%), occurred on the day of vaccination (98%), and occurred after dose 1 (82%); most individuals had a history of allergies (78%) and had symptom onset within 30 minutes (87%). The estimated incidence rate of confirmed anaphylaxis was 4.8 (95% CI, 3.2-6.9) per million BNT162b2 doses and 5.1 (95% CI, 3.3-7.6) per million mRNA-1273 doses.

During the 21 days after vaccination, 12 individuals received a diagnosis of acute respiratory distress syndrome, 6 of multisystem inflammatory syndrome, and 29 of narcolepsy; follow-up will continue through 84 days after vaccination.

Table 4. Confirmed Myocarditis/Pericarditis After Receipt of mRNA Vaccines Compared With Vaccinated Comparators Among Individuals Aged 12-39 Years by Dose and Risk Interval, December 14, 2020-June 26, 2021

| Risk interval, d[a] | Dose | Events in risk interval (events/million person-years)[b] | Events in 21-d comparison interval[b,c] (events/million person-years)[b,c] | Adjusted rate ratio (95% CI)[d] | 2-Sided *P* value | Excess cases in risk interval per million doses (95% CI)[e] |
|---|---|---|---|---|---|---|
| 0-21 | Both | 34 (141.2) | 4 (35.0) | 3.75 (1.38 to 12.84) | .007 | 6.2 (2.3 to 7.8) |
| | 1 | 9 (70.4) | 4 (35.0) | 3.67 (0.92 to 17.35) | .07 | 3.1 (-0.4 to 4.0) |
| | 2 | 24 (221.3) | 4 (44.6) | 4.07 (1.45 to 14.18) | .005 | 10.1 (4.1 to 12.4) |
| 0-7 | Both | 29 (320.8) | 4 (35.0) | 9.83 (3.35 to 35.77) | <.001 | 6.3 (4.9 to 6.8) |
| | 1 | 5 (104.2) | 3 (35.0) | 7.27 (1.29 to 50.15) | .02 | 2.0 (0.5 to 2.2) |
| | 2 | 23 (565.9) | 4 (44.6) | 10.4 (3.54 to 37.76) | <.001 | 11.2 (8.9 to 12.1) |
| 8-14 | Both | 2 (25.7) | 4 (35.0) | 1.22 (0.14 to 7.74) | .82 | 0.1 (-3.0 to 0.4) |
| | 1 | 2 (48.0) | 3 (35.0) | 3.25 (0.31 to 29.64) | .30 | 0.6 (-2.0 to 0.9) |
| | 2 | 0 | 4 (44.6) | 0 (0 to 3.22) | .28 | -0.9 (-0.9 to 0) |
| 15-21 | Both | 3 (41.3) | 4 (35.0) | 1.55 (0.28 to 7.78) | .58 | 0.3 (-2.0 to 0.7) |
| | 1 | 2 (52.3) | 4 (35.0) | 2.58 (0.27 to 18.62) | .37 | 0.6 (-2.7 to 0.9) |
| | 2 | 1 (29.1) | 4 (44.6) | 0.67 (0.03 to 5.64) | .79 | -0.3 (-21.2 to 0.5) |

Abbreviation: mRNA, messenger RNA.

[a] In each "both" doses row, risk interval events were included if they occurred within the designated interval after either dose 1 or dose 2. In each row for dose 1, risk interval events were included if they occurred during the designated interval after dose 1; in each row for dose 2, risk interval events were included if they occurred during the designated interval after dose 2.

[b] For a given risk interval, the sum of the events in the dose 1 and 2 rows may not add up to the number of events in the rows for both doses owing to rigorous adjustment by calendar date, site, age, sex, and race and ethnicity, as described in the Methods. In every row, events were included only if, on the calendar day of the event, the risk and comparison intervals each included at least 1 vaccinated person in the same site, 5-year age group, sex, and race and ethnicity group (eFigure 1 in the Supplement). Similarly, events in the 21-day comparison interval column for dose 1 rows may differ from the number of events in the dose 2 rows.

[c] Comparison interval for all analyses was 22 to 42 days after either dose 1 or 2. Most comparator follow-up was 22 to 42 days after dose 2 but some was 22 to 42 days after dose 1 in individuals who had not received dose 2.

[d] Overall estimate from Poisson regression stratified by site, 5-year age group, sex, race and ethnicity, and calendar date.

[e] CIs for the excess risk estimates were based on the CIs of the corresponding adjusted rate ratios.

## Discussion

In this interim analysis of surveillance monitoring of more than 11.8 million doses of 2 mRNA vaccines in a diverse population and weekly analyses from December 14, 2020, to June 26, 2021, no vaccine-outcome association met the prespecified threshold for a signal. Incidence of selected serious outcomes was not significantly higher 1 to 21 days postvaccination compared with 22 to 42 days postvaccination for any of the outcomes. For the less frequent outcomes, CIs were wide and did not necessarily exclude clinically relevant increases associated with vaccination, and surveillance is ongoing.

This current surveillance complements other vaccine safety monitoring systems in the US, including the Vaccine Adverse Event Reporting System (VAERS) and v-safe.[21] Key strengths of this surveillance are that it is population based, geographically diverse, and updated weekly. Outcome incidence among vaccinees in a risk interval was compared with outcome incidence among similar vaccinees who were in their comparison interval on the same calendar date. Thus, the comparison group for each outcome event was similar in demographic characteristics to the case and was in follow-up on the same day at the same site, avoiding biases that can arise from variations in health care use during the pandemic, as well as day-to-day variations (eg, Sunday to Monday). In addition, the primary analyses focused on vaccinated rather than unvaccinated comparators. Every vaccinee contributed to the primary analyses by first contributing to the risk interval and then to the comparison interval. Individuals with recent vaccination were expected to be more similar to those with more remote vaccination than they were to unvaccinated individuals, which, over time, was expected to yield comparisons that were better balanced than were comparisons of vaccinees with unvaccinated comparators. Furthermore, access to comprehensive medical records permitted rapid case confirmation when appropriate.

In response to concerns regarding an association between thromboembolic outcomes with thrombocytopenia and ChAdOx1 nCoV-19 (AstraZeneca)[22,23] and Ad26.COV.2.S (Janssen) vaccines,[14,15] surveillance for additional outcomes (cerebral venous sinus thrombosis and thrombosis with thrombocytopenia syndrome) was initiated. There has been no evidence that these outcomes are associated with mRNA vaccines. Close monitoring will continue for thromboembolic outcomes with thrombocytopenia after vaccination with all COVID-19 vaccines, including the Ad26.COV.2.S vaccine.

Analyses of all ages combined did not detect a significant association between myocarditis/pericarditis and mRNA vaccines. However, consistent with case reports,[16,24] supplemental analyses of confirmed cases among individuals aged 12 to 39 years yielded an elevated RR estimate. Significant clustering within the first week after vaccination, especially after dose 2, provides additional evidence of an association between mRNA vaccines and myocarditis/pericarditis in younger individuals.

Anaphylaxis after COVID-19 mRNA vaccination has been observed more commonly than the estimated 1 to 2 cases per million doses reported after receipt of influenza vaccine and some other vaccines.[25] Estimated anaphylaxis incidence rates after receipt of both BNT162b2 and mRNA-1273 vaccines in this study were similar to rates after receipt of mRNA vaccines in other reports,[21,26] although somewhat higher than VAERS estimated reporting rates.[27] In contrast, estimated anaphylaxis incidence rates were much lower than the 24.7 cases of confirmed anaphylaxis per 100 000 vaccinees estimated through prospective surveillance of health care workers.[28] Consistent with reports from the European Union and Japan,[29] nearly all anaphylaxis after receipt of mRNA vaccines occurred among female recipients. Although the biological mechanism for the higher incidence among female vaccinees is not clear, it may be related to genes, hormones, and environmental and immunologic factors.[30]

The phase 3 trials for both the BNT162b2 and mRNA-1273 vaccines noted that the incidence of Bell palsy was higher in the vaccine group than in the placebo group.[3,4] Among nearly 40 000 vaccinees in both trials combined, there were 7 cases of Bell palsy vs 1 in the placebo group, corresponding to an RR of 7 ($P$ = .07).[31] In this current surveillance, neither the primary analyses nor those with unvaccinated comparators found evidence of an association between Bell palsy and mRNA vaccines, a finding that is consistent with a recent analysis of cases reported to the World Health Organization database.[32]

## Limitations

This study has several limitations. First, the statistical power of these early analyses was limited, especially for the less frequent outcomes. The 95% CIs around some of the RR estimates were wide and included clinically relevant risks. Six outcomes in the primary analyses yielded CIs that included RR estimates greater than 2.0, levels that may be clinically important even if outweighed by the COVID-19 outcomes prevented. During the next few months, the precision of the RR estimates will improve as follow-up accumulates. Second, vaccinees contributed follow-up in the risk interval before they contributed it in the comparison interval, and bias might arise if unmeasured variables associated with earlier vaccination were also associated with having an outcome. Third, there may be interest in specific outcomes that were not initially included or were included within a much broader category. However, additional outcomes were added in response to emerging concerns. Fourth, risk may be underestimated or missed if the real risk interval was modestly longer (ie, 1 week) beyond 21 days after exposure to a first or second dose or perhaps several weeks longer. Fifth, although vaccinees were followed for several months after vaccination, possible longer-term risks of vaccination were not being monitored. Sixth, only medically attended outcomes were included; thus, analyses could have underestimated risk if health care was not sought. Although the outcomes monitored are serious and usually associated with seeking care, anaphylaxis incidence may have been underestimated if individuals either received care in alternate settings or self-treated at the event.

**Table 5. Confirmed Anaphylaxis Cases After Medical Record Review Through May 29, 2021[a]**

| | No. (%) | |
|---|---|---|
| | BNT162b2 (n = 30) | mRNA-1273 (n = 25) |
| Age, mean (SD), y | 42.8 (14.5) | 45.7 (15.5) |
| Female sex | 30 (100) | 22 (88) |
| Time from vaccination to symptom onset, median (IQR) [N], min[b] | 10.0 (5.0-20.0) [21] | 10.0 (5.0-20.5) [20] |
| Time to symptom onset, min | | |
| ≤15[b] | 19 (63) | 17 (68) |
| ≤30[b] | 26 (87) | 22 (88) |
| History | | |
| Allergies[c] | 24 (80) | 19 (76) |
| Anaphylaxis[d] | 15 (50) | 5 (20) |
| Dose | | |
| 1 | 25 (83) | 20 (80) |
| 2 | 5 (17) | 5 (20) |
| Brighton Collaboration case definition level[e] | | |
| 1, High certainty | 13 (43) | 6 (24) |
| 2, Moderate certainty | 17 (57) | 18 (72) |
| 3, Low certainty | 0 | 1 (4) |
| Confirmed anaphylaxis cases per million doses (95% CI)[f] | 4.8 (3.2-6.9) | 5.1 (3.3-7.6) |
| Confirmed anaphylaxis cases per million doses among female individuals (95% CI)[f] | 8.9 (6.0-12.7) | 8.6 (5.2-12.5) |

[a] Includes 11 cases identified through internal diagnostic codes, 5 after vaccination with BNT162b2 and 6 after mRNA-1273.

[b] Although exact timing was not available for all cases, it was classifiable as within 15 or 30 minutes for all cases, according to available notes in the medical record. For example, symptom onset was noted as beginning "shortly after" vaccination for 2 cases; these were classified as symptom onset within 30 minutes.

[c] History of allergies included other vaccine (n = 8), bee sting (n = 4), nuts (n = 7), other food (n = 15), food additive (n = 2), antibiotic (n = 25), contrast (n = 3), other medication (n = 23), latex (n = 8), and cats (n = 1). Additionally, 1 person was noted as having an allergy to polyethylene glycol.

[d] History of anaphylaxis included other vaccine (n = 3), bee sting (n = 4), nuts (n = 3), other food (n = 5), food additive (n = 2), antibiotic (n = 7), contrast (n = 2), other medication (n = 5), and latex (n = 1).

[e] The Brighton criteria required that the patient experienced sudden onset of anaphylaxis after vaccination, had rapid progression of signs and symptoms, had involvements of multiple (2 or more) organ systems, and had no clear alternative etiology or diagnosis for the event. The case definition is further divided into 3 levels of diagnostic certainty based on specific signs/symptoms and organ systems involved, with level 1 being the highest level of certainty.

[f] Cases classified as Brighton level 1, 2, or 3 after adjudication were considered confirmed.

## Conclusions

In interim analyses of surveillance of mRNA COVID-19 vaccines, incidence of selected serious outcomes was not significantly higher 1 to 21 days postvaccination compared with 22 to 42 days postvaccination. While CIs were wide for many outcomes, surveillance is ongoing.

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