# Safety of COVID-19 mRNA Vaccination Among Young Children in the Vaccine Safety Datalink

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We previously assessed safety of monovalent messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccines using weekly surveillance monitoring known as rapid cycle analysis (RCA) among individuals aged 5 years and older, identifying an increased risk for myocarditis and pericarditis in younger males, particularly following dose 2 of the primary series.[1–3] Information regarding COVID-19 vaccine safety among children under age 5 is limited.[4] Here we report RCA safety surveillance of mRNA COVID-19 vaccines administered in this youngest age group within the Vaccine Safety Datalink (VSD).

## METHODS

VSD is a collaboration between the Centers for Disease Control and Prevention and 8 data-contributing health systems (Kaiser Permanente: Colorado, Northern California, Northwest, Southern California, and Washington; Marshfield Clinic; Health Partners; and Denver Health), with approximately 550 000 children under age 5 years.[5] VSD sites maintain comprehensive electronic medical records for their members, including COVID-19 vaccination data from retail pharmacies and state immunization registries.[6]

For our active, population-based RCA safety surveillance we performed sequential analyses on data that was updated weekly for 23 prespecified safety outcomes ($n = 19$, including myocarditis and pericarditis and seizures) and descriptive monitoring ($n = 4$, including anaphylaxis) (Supplemental Table 3).

We compared outcomes after any mRNA vaccine dose among primary series vaccinees in a risk interval (1–21 days postvaccination) with outcomes among primary series vaccinated comparators who were concurrently (on the same calendar day), in the comparison interval (22–42 days postvaccination), using methods previously described.[1] For seizures, risk intervals were prespecified as 0 to 7 and 0 to 21 days postvaccination. We estimated adjusted rate ratios (RRs) and corresponding 95% confidence intervals (CIs) using Poisson regression, adjusting for age, race, sex, site, and calendar day.[1] Assuming 1 year of weekly monitoring with uneven vaccine uptake over time, we prespecified a signaling threshold of a 1-sided $P$ value $< .011$. We reviewed medical records of all cases of myocarditis and pericarditis, anaphylaxis, and other selected outcomes (Supplemental Table 3).[1]

Surveillance was approved by institutional review boards at all participating sites with a waiver of informed consent.

## RESULTS

From June 18, 2022 to March 18, 2023, 135 005 doses of Pfizer-BioNTech COVID-19 vaccine were given to children aged 6 months to 4 years, and 112 006 doses of Moderna COVID-19 vaccine were given to children aged 6 months to 5 years in the VSD population (Table 1). For most outcomes, including myocarditis and pericarditis, no events occurred in the risk interval (Table 2). RRs were not elevated

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**TABLE 1** Vaccine Doses Administered in the Vaccine Safety Datalink to Children Aged 6 Months to <5 Years, June 18, 2022 Through March 18, 2023

| Characteristic | Number of Doses Administered | |
|---|---|---|
| | Pfizer-BioNTech,[a] *n* (%) | Moderna,[b] *n* (%) |
| Total | 135 005 | 112 006 |
| Dose 1 | 60 134 (45) | 59 872 (53) |
| Dose 2 | 50 903 (38) | 52 134 (47) |
| Dose 3 | 23 968 (18) | NA |
| Sex | | |
| Female | 66 343 (49) | 55 228 (49) |
| Male | 68 662 (51) | 56 778 (51) |
| Age | | |
| 6 mo–<1 y | 17 081 (13) | 16 566 (15) |
| 1–<2 y | 25 979 (19) | 22 062 (20) |
| 2–<3 y | 27 791 (21) | 22 510 (20) |
| 3–<4 y | 31 218 (23) | 22 708 (20) |
| 4–<5 y | 32 936 (24) | 23 428 (21) |
| 5–<6 y | NA | 4732 (4) |
| Race and ethnicity[c] | | |
| American Indian/Alaskan Native | 305 (<1) | 225 (<1) |
| Asian | 34 528 (26) | 26 903 (24) |
| Black, Non-Hispanic | 4260 (3) | 3105 (3) |
| Hispanic/Latino | 26 543 (20) | 19 482 (17) |
| Native Hawaiian/Pacific Islander | 817 (<1) | 498 (<1) |
| White, non-Hispanic | 42 158 (31) | 39 944 (36) |
| Multiple or other | 8022 (6) | 5940 (5) |
| Unknown | 18 372 (14) | 15 909 (14) |

NA, not applicable.
[a] The Pfizer-BioNTech vaccine is authorized for use in children 6 mo to <5 y of age as a 3-dose series with dose 1 and dose 2 given 21 d apart, and dose 3 given 2 mo following dose 2. Only monovalent dose 3′s are included in this surveillance; bivalent doses are monitored in separate VSD safety surveillance.
[b] The Moderna vaccine is authorized for use in children 6 mo to <6 y of age as a 2-dose series with dose 1 and dose 2 given 28 d apart.
[c] VSD 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).

for any prespecified outcomes following any dose of Pfizer-BioNTech and Moderna vaccine, and none of the outcomes met the signaling threshold of $P < .011$. For example, the RR for convulsions and seizures in 0 to 7 days postvaccination was 0.64 (95% CI: 0.25–1.51, $P = .89$) after Pfizer-BioNTech and 0.85 (95% CI: 0.27–2.32, $P = .70$) after Moderna. One case of hemorrhagic stroke and 1 case of pulmonary embolism were identified after vaccination; however, chart review found each outcome was unrelated to vaccination (both children had congenital abnormalities).

In descriptive analyses, 1 case of anaphylaxis was found unrelated to vaccination (food allergy). One case of multisystem inflammatory syndrome in children (MIS-C) was identified postvaccination, but chart review found the child developed COVID-19 infection after vaccination and before MIS-C diagnosis.

## DISCUSSION

In this interim analysis of children aged 5 years and younger, safety surveillance of more than 245 000 COVID-19 mRNA vaccine doses over 9 months did not detect a safety signal for any outcome during the 21 days after vaccination. Importantly, no cases of myocarditis or pericarditis occurred after vaccination. This safety profile is consistent with results from phase 3 clinical trials and other vaccine safety monitoring systems.[4]

Strengths of this study included a diverse population, weekly analyses, and robust capture of outcome and vaccination data. Limitations include reduced statistical power of early analyses, particularly for rare outcomes. Also, vaccine uptake in the evaluated age group was low; only 24.7% of the eligible VSD population received at least 1 vaccine dose (ranging from 6.6% to 30.2% across VSD sites), although uptake was higher than that reported for this age group in other US populations (~5.9% to 8.8%).[7] Additionally, RCA surveillance focused on prespecified medically-attended, serious safety outcomes and did not include all potential safety concerns. Furthermore, we may have underestimated or missed potential safety concerns if the biologically plausible risk interval for an outcome differed from our specified risk interval.



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**TABLE 2** Outcomes Among Vaccinees During the 1 Through 21 Day Risk Interval After Any Dose of COVID-19 mRNA Vaccine, Compared on the Same Calendar Day With Outcomes Among Vaccinated Individuals 22 to 42 Days After Their Most Recent Dose, June 18, 2022 Through March 18, 2023

| Outcome[b] | Risk Interval | Vaccine Type | Events in Risk Interval | Events in Comparison Interval (22–42 d) | Crude/ Adjusted Expected Counts[a] | Adjusted Rate Ratio (95% CI)[c] | 1-Sided *P* | Signal[d] |
|---|---|---|---|---|---|---|---|---|
| Appendicitis | 1–21 d | Pfizer-BioNTech | 1 | 1 | 0.9/2.1 | 0.49 (0.01–26.53) | .91 | No |
| | | Moderna | 0 | 1 | 1.5/NE | 0.00 (0.00–12.67) | .40 | No |
| Bell's Palsy | 1–21 d | Pfizer-BioNTech | 0 | 1 | 0.5/NE | 0.00 (0.00–38.00) | .67 | No |
| | | Moderna | 1 | 0 | 0.0/NE | NE (0.06–∞) | .49 | No |
| Encephalitis, myelitis, or encephalomyelitis | 1–21 d | Pfizer-BioNTech | — | — | — | — | — | — |
| | | Moderna | 1 | 0 | 0.0/NE | NE (0.02–∞) | .74 | No |
| Guillain-Barre syndrome | 1–21 d | Pfizer-BioNTech | — | — | — | — | — | — |
| | | Moderna | 0 | 1 | 0.7/NE | 0.00 (0.00–26.75) | .59 | No |
| Immune thrombocytopenia | 1–21 d | Pfizer-BioNTech | 0 | 1 | 1.0/NE | 0.00 (0.00–18.77) | .50 | No |
| | | Moderna | 1 | 1 | 0.8/0.9 | 1.14 (0.03–44.34) | .72 | No |
| Kawasaki disease | 1–21 d | Pfizer-BioNTech | 2 | 1 | 1.1/1.0 | 2.05 (0.15–60.69) | .49 | No |
| | | Moderna | 0 | 3 | 5.8/NE | 0.00 (0.00–1.09) | .06 | No |
| Pulmonary embolism | 1–21 d | Pfizer-BioNTech | 1 | 0 | 0.0/NE | NE (0.08–∞) | .41 | No |
| | | Moderna | — | — | — | — | — | — |
| Seizures | 0–7 d | Pfizer-BioNTech | 9 | 24 | 9.5/14.0 | 0.64 (0.25–1.51) | .89 | No |
| | | Moderna | 5 | 19 | 5.4/5.9 | 0.85 (0.27–2.32) | .70 | No |
| | 0–21 d | Pfizer-BioNTech | 38 | 24 | 25.0/38.9 | 0.98 (0.56–1.71) | .59 | No |
| | | Moderna | 23 | 19 | 20.9/21.0 | 1.09 (0.57–2.11) | .46 | No |
| Stroke, hemorrhagic | 1–21 d | Pfizer-BioNTech | 1 | 1 | 1.1/0.9 | 1.12 (0.03–44.64) | .72 | No |
| | | Moderna | — | — | — | — | — | — |
| Transverse myelitis | 1–21 d | Pfizer-BioNTech | — | — | — | — | — | — |
| | | Moderna | 0 | 1 | 0.5/NE | 0.00 (0.00–38.00) | .67 | No |
| Venous thromboembolism | 1–21 d | Pfizer-BioNTech | — | — | — | — | — | — |
| | | Moderna | 0 | 1 | 0.5/NE | 0.00 (0.00–38.00) | .67 | No |

NE, not estimable. —, analysis not yet possible.

[a] Expected counts: crude estimate via indirect standardization and maximum likelihood estimate.

[b] Outcomes were only included in this table if there were events in either the risk or comparison interval for either vaccine type after any dose, making analyses possible. All outcomes under surveillance are listed in Supplemental Table 3. Safety monitoring by individual dose is ongoing, however, since very few outcomes have cases in either the risk or comparison interval only combined analyses are presented here.

[c] Stratified by Vaccine Safety Datalink site, age (year), sex, race and ethnicity, and calendar date.

[d] Signal defined as 1-sided $P < 0.011$.

These results can provide reassurance to clinicians, parents, and policymakers alike. Surveillance is ongoing.


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## ABBREVIATIONS

CI: confidence interval
COVID-19: coronavirus disease 2019
mRNA: messenger ribonucleic acid
RR: rate ratio
VSD: Vaccine Safety Datalink


reviewed by CDC and was conducted consistent with applicable federal law and CDC policy. See, for example, 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.

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