HHS Public Access

Author manuscript

Pediatrics. Author manuscript; available in PMC 2024 May 01.

Published in final edited form as:

Pediatrics. 2023 July 01; 152(1): . doi:10.1542/peds.2023-061894.

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

Kristin Goddard, MPH[a], **James G. Donahue, DVM, PhD**[b], **Ned Lewis, MPH**[a], **Kayla E. Hanson, MPH**[b], **Eric S. Weintraub, MPH**[c], **Bruce Fireman**[a], **Nicola P. Klein, MD, PhD**[a]

[a]Kaiser Permanente Vaccine Study Center, Kaiser Permanente Northern California, Oakland, California;

[b]Marshfield Clinic Research Institute, Marshfield, Wisconsin;

[c]Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, Georgia

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 5 19, including myocarditis and pericarditis and seizures) and descriptive monitoring (n 5 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

Address correspondence to Nicola Klein, MD, PhD, 1 Kaiser Plaza Oakland, CA 94612. nicola.klein@kp.org.

Ms Goddard, Mr Lewis, and Mr Weintraub were responsible for conceptualization and study design, acquisition of data, and analyses and interpretation; Dr Donahue and Ms Hanson were responsible for acquisition of data and its analysis and interpretation; Mr Fireman and Dr Klein were responsible for conceptualization, study design, analyses, and interpretation; and all authors critically reviewed and revised the manuscript for important intellectual content, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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 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* 5 .89) after Pfizer-BioNTech and 0.85 (95% CI: 0.27–2.32, *P* 5 .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 from6.6% 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.

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We thank all VSD site investigators, project managers, data managers, and medical record abstractors for their contributions to this project.

FUNDING:

This study was supported by the Centers for Disease Control and Prevention (CDC), contract number 200-2012-53581-0011. This activity was 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.

CONFLICT OF INTEREST DISCLOSURES:

Dr Donahue received funding from Janssen Vaccines and Prevention for a study unrelated to coronavirus disease 2019 vaccines; Dr Klein received grants from Pfizer for coronavirus disease 2019 vaccine clinical trials and from Merck, GSK, and Sanofi Pasteur for study work unrelated to the current study work. The remaining authors have no conflicts of interest to disclose.

ABBREVIATIONS

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

REFERENCES

1. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. JAMA. 2021;326(14):1390–1399 [PubMed: 34477808]
2. Hause AM, Baggs J, Marquez P, et al. COVID-19 vaccine safety in children aged 5–11 years - United States, November 3-December 19, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(5152):1755–1760 [PubMed: 34968370]
3. Goddard K, Hanson KE, Lewis N, Weintraub E, Fireman B, Klein NP. Incidence of myocarditis/pericarditis following mRNA COVID-19 vaccination among children and younger adults in the United States. Ann Intern Med. 2022;175(12):1169–1771 [PubMed: 36191323]
4. Hause AM, Marquez P, Zhang B, et al. COVID-19 mRNA vaccine safety among children aged 6 months-5 years - United States, June 18,2022-August 21, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(35): 1115–1120 [PubMed: 36048728]
5. Baggs J, Gee J, Lewis E, et al. The vaccine safety Datalink: a model for monitoring immunization safety. Pediatrics. 2011;127(suppl 1):S45–S53 [PubMed: 21502240]
6. Groom HC, Crane B, Naleway AL, et al. Monitoring vaccine safety using the vaccine safety Datalink: assessing capacity to integrate data from Immunization Information systems. Vaccine. 2022;40(5):752–756 [PubMed: 34980508]

7. Centers for Disease Control and Prevention. Demographic characteristics of people receiving COVID-19 vaccinations in the United States. Available at: https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends. Accessed October 18, 2022

TABLE 1

Vaccine Doses Administered in the Vaccine Safety Datalink to Children Aged 6 Months to <5 Years, June 18, 20 22 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).

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	54/5.9	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 $P < 0.011$.