Protection from COVID-19 vaccination and prior SARS-CoV-2 infection among children aged 6 months – 4 years, United States, September 2022–April 2023

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Summary: Children <5 years with prior infection had lower risk of SARS-CoV-2 compared to those without. There was no difference in incidence by vaccination status. While COVID-19 vaccines reduce severe disease, they may not reduce overall SARS-CoV-2 infections in young children.

Abstract

To understand how COVID-19 vaccines impact infection risk in children <5 years, we assessed risk of SARS-CoV-2 infection from Sept 2022–April 2023 in three cohort studies. There was no difference in risk by vaccination status. While vaccines reduce severe disease, they may not reduce SARS-CoV-2 infections in young children.

Key words: COVID-19, vaccination, prior infection, children, SARS-CoV-2

Introduction

As of October 15, 2024, 966 COVID-19-associated deaths have been reported among children aged 6 months – 4 years in the United States [1]. While COVID-19 vaccines were first authorized in June 2022 for children aged 6 months – 4 years to prevent severe outcomes from COVID-19, data on their real-world effectiveness in this age group remain scarce [2-5]. Understanding how well young children are protected by COVID-19 vaccines and prior infection is important for informing and adapting public health strategies and policies, particularly as new variants of varying transmissibility and illness severity emerge.

Using merged data from three prospective cohort studies in the United States, we estimated risk of any SARS-CoV-2 infection (asymptomatic and symptomatic) and symptomatic infection (i.e., COVID-19), during an Omicron XBB predominant period to better understand protection offered by both vaccination and prior infection among children 6 months – 4 years of age.

Methods:

Study population and data collection

From September 1, 2022 – April 30, 2023, three prospective cohort studies in the United States (PROTECT, CASCADIA, and CoVE) collected data that were combined for this analysis [6-8]. Children aged 6 months – 4 years living in Washington, Oregon, Michigan, Arizona, and Utah, including individuals from the same household, were eligible for inclusion. Study design, data and specimen collection, and laboratory testing have been described previously [8] (Supplemental Methods).

Patient Consent Statement

Informed written consent was obtained from a parent or guardian of the enrolled child. These studies were reviewed by CDC and approved by the Institutional Review Boards at participating sites and Abt Associates and were conducted consistent with applicable federal law and CDC policy.[1]

Statistical analysis

Descriptive statistics were used to compare participants who became infected to participants who remained uninfected based on RT-PCR results. Statistics were also compared between those who were unvaccinated to those who, at a minimum, had completed their primary series (at least 2 doses of Moderna or at least 3 doses of Pfizer-BioNTech, including both original [non-Omicron containing] and bivalent [Omicron-containing] vaccines). Those who had received a combination of Moderna and Pfizer-BioNTech vaccines were excluded (n=8), (Supplementary Methods). P-values were calculated using chi-square tests for categorical variables and Wilcoxon tests for continuous variables at the p-value <0.01 level. Prior infection was defined as laboratory-confirmation of infection by RT-PCR from a study-collected specimen, positive anti-N SARS-CoV-2 antibody, or self-report of infection prior to enrollment or September 1, 2022 (whichever occurred later). Unadjusted SARS-CoV-2 incidence rates per 1,000 person-days and adjusted hazard ratios were calculated separately for the outcomes of infection (defined as a positive RT-PCR SARS-CoV-2 test regardless of symptoms) and COVID-19 illness (defined as a positive RT-PCR test and ≥2 COVID-like illness symptoms reported within seven days before or after the specimen collection date); 95% confidence intervals (CIs) for incidence were calculated using the Jeffreys method [9]. Rates were stratified by vaccination status, prior infection status, and vaccine manufacturer. Hazard ratios with robust standard errors were adjusted for age (continuous) and underlying conditions (0 or ≥1), and geographic site and race/ethnicity when sample size allowed.

[1] 45 C.F.R. part 46, 21 C.F.R. part 56, 42 U.S.C. Sect. 241(d), 5 U.S.C. Sect. 552a, 44 U.S.C. Sect. 3501 et seq.

Person-days were accrued until the time of the first event, withdrawal date, or the end of the study period. The surveillance weeks for which there was no specimen result (e.g., participant skipped a weekly swab) or the specimen failed molecular testing were not censored. Participants could contribute to more than one vaccination category since vaccination status is time-varying. All analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC) or R software (version 4.3.0; R Core Team).

Results:

Between September 1, 2022, and April 30, 2023, 614 children contributed 84,329 person-days (median follow-up time: 154 days, IQR: 77, 199) to the study (Table 1). Median adherence to weekly swabbing throughout the study period was 92% (IQR: 80-98%). Overall, 50.2% of participants were female, the median age at study entry was 3 years (interquartile range [IQR]: 1.8-4 years), and the majority were White non-Hispanic (62.4%). By the end of the study period, 28.5% (n=175) of participants were unvaccinated, 15.3% (n=94) were partially vaccinated, and 56.2% (n=345) had completed, at a minimum, their primary vaccine series; of those 345, 129 received a booster dose (37%) and 139 (40%) received at least one bivalent dose. Prior to enrollment in the study, 41.9% of participants had a SARS-CoV-2 infection, half of whom had also received at least their primary vaccine series (47.1%). During the study period, 87 (14.2%) of 614 participants had a laboratory-confirmed SARS-CoV-2 infection; 33 (37.9%) of 87 had symptomatic infections. Genetic sequencing results were available for 46 (53%) of the SARS-CoV-2 infections. The most prevalent lineages were XBB (37.0%), BA.4 or BA.5 (28.3%), BQ.1.1 (19.6%), BQ.1 (13.0%), and BA.2.75 (2.2%).

Participants with evidence of prior SARS-CoV-2 infection were less likely to be infected with SARS-CoV-2 and experience symptomatic COVID-19 compared with those who had no evidence of prior infection

(Hazard Ratio [HR]: 0.28 [95%CI: 0.16-0.49] and HR: 0.21 [95%CI: 0.08-0.54]), Table 2. This was true regardless of timing of prior infection. In addition, those with prior infection and who were vaccinated, were less likely to be infected (HR: 0.31 [95%CI: 0.13-0.77]), including those vaccinated ≥60 days prior (HR: 0.29 [95%CI: 0.10-0.80]) than those who were unvaccinated and naïve.

There was no difference in risk of infection or symptomatic COVID-19 by vaccination status alone, regardless of timing of vaccination or manufacturer type. However, naïve participants vaccinated with Pfizer-BioNTech were more likely to be infected and experience symptomatic COVID-19 compared to naïve and unvaccinated participants (HR: 2.59 [95%CI: 1.27-5.28]), whereas participants with evidence of prior infection and who were vaccinated with Pfizer-BioNTech were less likely to be infected (HR: 0.22 [95%CI: 0.05-0.95]).

Discussion

Although there was no difference in risk of SARS-CoV-2 infection and symptomatic COVID-19 among children aged 6 months - 4 years by vaccination status, prior infection with SARS-CoV-2 was associated with lower incidence of both. These findings suggest that prior SARS-CoV-2 infection provides protection against both overall SARS-CoV-2 infection and COVID-19.

Two previous studies among children <5 years have shown that vaccination protects against symptomatic illness [2, 3]. Although genetic sequencing was only available for 53% of specimens, it is notable that the most common variant identified in any infections in this study was XBB (n=17), an Omicron subvariant with substantial genetic variation from those strains included in the monovalent or bivalent vaccines administered to this group. This may partly explain the differences between those earlier studies and the findings in this study. Importantly, the outcomes of infection and symptomatic

COVID-19 as defined in these cohorts represent predominantly non-severe disease; protection against more severe outcomes such as ED visits and hospitalization have been demonstrated in this age group [10]. Therefore, while our results are important for understanding risk of infection, vaccination is still an important tool for protecting children from severe COVID-19.

Interestingly, among participants without evidence of prior infection, those vaccinated with Pfizer-BioNTech were more likely to have SARS-CoV-2 infection and COVID-19 compared to those who were naïve and unvaccinated. This may be partly due to the fact that only 28% of children who were vaccinated with Pfizer-BioNTech received a bivalent Omicron-containing Pfizer-BioNTech vaccine, either as the third dose of the primary series (80.6%) or as an additional booster (19.4%). Further research is needed to assess vaccine effectiveness against infection for this age group for updated 2023-2024 vaccines.

Prior infection plus vaccination may provide the strongest immunity; however more follow-up is needed in this age group to determine the relative impact of cumulative immunologic experiences from both infection and vaccination. Other studies have demonstrated that hybrid immunity provides better protection than prior infection or vaccination alone [2, 11]. This finding reflects similar phenomena seen in influenza, where infection followed by vaccination produces a broader immune response than either intervention alone [12], however it is important to note that contracting a primary infection in a naïve immune system poses a risk of severe events such as hospitalization and death, shown by much larger, randomized, studies [10].

The major limitation of this study was lack of sample size which precluded us from estimating vaccine effectiveness and adjusting for all potential confounders, such as proportion of circulating variant and 7-

day incidence average by site, daycare attendance, and whether household members tested positive for SARS-CoV-2. Other limitations of this study, most notably, the potential for missed prior infection detections due to waning of anti-N SARS-CoV-2 antibodies, have been previously described [8].

Conclusion

Despite the limitations, data from this community cohort of young children with any SARS-CoV-2 infections and symptomatic COVID-19 disease contribute to understanding protection from vaccination and prior infection. COVID-19 vaccines are recommended to reduce severe illness; overall risk of infection may not differ substantially between vaccinated and unvaccinated children <5 years.

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Role of the Funder/Sponsor: The CDC collaborated with partner sites to design and conduct the study; managed, analyzed, and interpreted the data; prepared, reviewed, and approved the manuscript; and had a role in the decision to submit the manuscript for publication.

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Table 1. Characteristics of participants aged 6 months – 4 years by laboratory-confirmed SARS-CoV-2 and COVID-19 mRNA vaccination status, Sept 1, 2022 – April 30, 2023.

	Overall		SARS-CoV-2 positive during the study period		SARS-CoV-2 negative		Positive vs. negative	Unvaccinated		Completed at least primary series[a]		Unvaccinated vs. at least primary series
	No.	(Col %)	No.	(Row%)	No.	(Row%)	p-value	No.	(Row%)	No.	(Row%)	p-value
Total	614		87	14.2	527	85.8		175	28.5	345	56.2	
Cohort site[b]							0.0592					<0.001
PROTECT: Arizona	185	30.1	27	14.6	158	85.4		84	45.4	55	29.7	
PROTECT: Utah	67	10.9	12	17.9	55	82.1		37	55.2	18	26.9	
CASCADIA: Oregon	185	30.1	19	10.3	166	89.7		34	18.4	135	73.0	
CASCADIA: Washington	137	22.3	18	13.1	119	86.9		9	6.6	115	83.9	
CoVE: Michigan	40	6.5	11	27.5	29	72.5		11	27.5	22	55.0	
Sex							0.3993					0.051
Female	308	50.2	40	13.0	268	87.0		80	26.0	189	61.4	
Male	306	49.8	47	15.4	259	84.6		95	31.0	156	51.0	

Age median (IQR)	3.0	1.8-4.0	3.2	1.4-4.0	3.0	1.9-4.0	0.0679	3.0	1.9-4.0	3.0	1.8-4.0	0.054
Race/Ethnicity[c]							0.4852					<0.001
White NH	383	62.4	56	14.6	327	85.4		97	25.3	231	60.3	
Hispanic	89	14.5	9	10.1	80	89.9		38	42.7	33	37.1	
Multiple races NH	84	13.7	11	13.1	73	86.9		11	13.1	61	72.6	
Other NH	58	9.4	11	19.0	47	81.0		29	50.0	20	34.5	
Chronic Conditions[d]							0.1800					0.539
None	577	94.0	79	13.7	498	86.3		163	28.2	326	56.5	
1 or more	37	6.0	8	21.6	29	78.4		12	32.4	19	51.4	
Individuals living in participants' household							0.6329					0.263
2	17	2.8	3	17.6	14	82.4		4	23.5	9	52.9	
3	128	20.8	15	11.7	113	88.3		30	23.4	80	62.5	
≥4	469	76.4	69	14.7	400	85.3		141	30.1	256	54.6	
Children living in participants' household							0.1434					0.003
1	128	20.8	13	10.2	115	89.8		22	17.2	82	64.1	

≥2	486	79.2	74	15.2	412	84.8		153	31.5	263	54.1	
Swab adherence median (IQR)	92	80-98	92	83-97	92	80-100	0.6780	93	75-100	91	83-97	0.814
Swab adherence							0.2291					0.017
<80%	144	23.5	16	11.1	128	88.9		52	36.1	70	48.6	
>=80%	470	76.5	71	15.1	399	84.9		123	26.2	275	58.5	
Time since prior infection[e,f]							0.0021					0.008
No prior infection	357	58.1	68	19.0	289	81.0		82	23.0	224	62.7	
<4 months	95	15.5	7	7.4	88	92.6		33	34.7	43	45.3	
4-<6 months	34	5.5	3	8.8	31	91.2		9	26.5	21	61.8	
6-<12 months	113	18.4	8	7.1	105	92.9		45	39.8	49	43.4	
≥12 months	15	2.4	1	6.7	14	93.3		6	40.0	8	53.3	
Prior infection[f]							<.0001					<0.001
None	357	58.1	68	19.0	289	81.0		82	23.0	224	62.7	
1 or more	257	41.9	19	7.4	238	92.6		93	36.2	121	47.1	

RT-PCR	127	49.4	6	4.7	121	95.3		66	52.0	34	26.8	
Serology	76	29.6	9	11.8	67	88.2		20	26.3	50	65.8	
Self-report	54	21.0	4	7.4	50	92.6		7	13.0	37	68.5	
Symptomatic COVID-19[g]												0.539
No			54	62.1				19	35.2	33	61.1	
Yes			33	37.9				8	24.2	19	57.6	
Predominant variant period of infection[h]												0.026
BA.4/BA.5[i]			55	63.2				21	38.2	27	49.1	
XBB[j]			32	36.8				6	18.8	25	78.1	

Abbreviations: Col = column; IQR = interquartile range; PCR = *polymerase chain reaction*.

[a]Participants completed at least a primary vaccination series (2 doses of Moderna or three doses of Pfizer-BioNTech) and may have also received bivalent doses. Participants with partial vaccination were excluded from those who completed at least a primary series (1 dose of Moderna or less than three doses of Pfizer-BioNtech), n=79.

[b]Florida and Texas sites from PROTECT were excluded because no children <5 years of age were vaccinated.

[c]The 'Other, non-Hispanic' category includes participations who identified as American Indian non-Hispanic, Alaska Native non-Hispanic, Asian non-Hispanic, Black and African American non-Hispanic, and Native Hawaiian/Pacific Islander non-Hispanic.

[d]Chronic conditions for PROTECT included asthma, chronic lung disease, cancer, diabetes, obesity, heart disease, hypertension, kidney disease, immunosuppression, liver disease, neurologic or neuromuscular disease, and autoimmune disease; and for CASCADIA and CoVE included: asthma, heart disease, sleep apnea, down syndrome, diabetes, cancer, autoimmune disease, liver disease, kidney disease, hematological disease, neurologic or neuromuscular disease, stroke, deep vein thrombosis or pulmonary embolism, anxiety, depression, immunosuppression, hypertension and thyroid disease.

[e]Prior infection was defined as laboratory-confirmation of infection by RT-PCR from a study-collected specimen, positive anti-N SARS-CoV-2 antibody, or self-report of infection prior to enrollment or September 1, 2022.

[f]Time since prior infection was calculated as the date of the most recent prior infection to the first week each participant was included in the analysis.

[g]Symptomatic COVID-19 was defined as those with a positive RT-PCR test and at least two COVID-like illness symptoms reported within seven days of the specimen collection date.

[h]Time period in which the positive SARS-CoV-2 infection occurred.

[i]BA.4/BA.5 predominant period was defined as September 1, 2022 – January 28, 2023.
[j]XBB predominant period was defined as January 29, 2023 – April 30, 2023.

Table 2. Incidence and adjusted hazard ratios of laboratory-confirmed SARS-CoV-2 infection and symptomatic COVID-19 among children aged 6 months – 4 years by vaccine type and interval since receipt of a bivalent vaccine dose.

Vaccination and prior infection status	Contributing participants[a]	Days since most recent vaccine dose, median (IQR)	Any SARS-CoV-2 infections	Unadjusted incidence of any SARS-CoV-2 infections per 1000	Adjusted hazard ratio (95% CI)[c]	Symptomatic COVID-19[b]	Unadjusted incidence of symptomatic COVID-19 Per 1,000	Adjusted hazard ratio (95% CI)[d]
Prior infection status								
Naïve[e]	357	98 (54, 150)	68	1.48 (1.16, 1.87)	Ref	28	0.61 (0.41, 0.87)	Ref
Prior infection[f]	257	99 (53, 155)	19	0.48 (0.30, 0.73)	0.28 (0.16, 0.49)	5	0.13 (0.05, 0.28)	0.21 (0.08, 0.54)
Vaccination status, by manufacturer and timing of receipt								
Unvaccinated	202	-	27	1.00 (0.67, 1.43)	Ref	8	0.30 (0.14, 0.56)	Ref
Vaccinated[g]	345	100 (56, 152)	52	1.19 (0.90, 1.55)	1.23 (0.69, 2.16)	19	0.44 (0.27, 0.67)	1.61 (0.65, 4.03)
Vaccinated, including bivalent dose[h]	139	59 (34, 90)	11	1.04 (0.55, 1.81)	0.74 (0.37, 1.48)	5	0.47 (0.18, 1.04)	1.04 (0.37, 2.96)
Vaccinated, Moderna	216	104 (59, 158)	25	0.87 (0.57, 1.26)	0.87 (0.44, 1.71)	7	0.24 (0.11, 0.48)	0.91 (0.31, 2.69)
Vaccinated, Pfizer-BioNTech	129	92 (50, 142)	27	1.84 (1.24, 2.63)	1.67 (0.91, 3.07)	12	0.82 (0.45, 1.38)	2.91 (1.12, 7.53)
Vaccinated, within 60 days	260	37 (23, 48)	10	0.85 (0.44, 1.50)	0.95 (0.40, 2.24)	4	0.34 (0.11, 0.80)	1.34 (0.36, 5.04)
Vaccinated ≥60 days	323	127 (92, 171)	42	1.32 (0.97, 1.77)	1.34 (0.75, 2.41)	15	0.47 (0.28, 0.76)	1.72 (0.69, 4.32)
Vaccination and prior infection status								
Unvaccinated, naïve	94	-	15	1.36 (0.80, 2.19)	Ref	5	0.45 (0.17, 1.00)	Ref
Unvaccinated, prior infection	108	-	12	0.75 (0.41, 1.26)	0.58 (0.25, 1.35)	3	0.19 (0.05, 0.50)	0.47 (0.10, 2.16)
Vaccinated, naïve	224	99 (56, 150)	45	1.64 (1.21, 2.18)	1.69 (0.85, 3.36)	17	0.62 (0.38, 0.97)	1.64 (0.49, 5.44)
Vaccinated, prior infection	121	101 (56, 156)	7	0.43 (0.19, 0.85)	0.31 (0.13, 0.77)	2	0.12 (0.03, 0.40)	0.31 (0.06, 1.65)

Vaccine manufacturer and prior infection status								
Unvaccinated, naïve	94	-	15	1.36 (0.80, 2.19)	Ref	5	0.45 (0.17, 1.00)	Ref
Vaccinated (Moderna), naïve	146	100 (58, 150)	20	1.03 (0.65, 1.56)	1.09 (0.49, 2.46)	5	0.26 (0.10, 0.56)	0.67 (0.16, 2.83)
Vaccinated (Moderna), prior infection	70	112 (63, 171)	5	0.53 (0.20, 1.16)	0.37 (0.13, 1.06)	2	0.21 (0.04, 0.68)	0.52 (0.10, 2.80)
Vaccinated (Pfizer-BioNTech), naïve	78	95 (51, 148)	25	3.13 (2.07, 4.54)	2.59 (1.27, 5.28)	12	1.50 (0.82, 2.54)	3.57 (1.10, 11.63)
Vaccinated (Pfizer-BioNTech), prior infection	51	88 (50, 136)	2	0.30 (0.06, 0.96)	0.22 (0.05, 0.95)	0	Not estimated	Not estimated
Timing of vaccination and prior infection status								
Unvaccinated, naïve	94	-	15	1.36 (0.80, 2.19)	Ref	5	0.45 (0.17, 1.00)	Ref
Vaccinated (<60 days), naïve	166	37 (23, 49)	8	1.07 (0.50, 2.01)	1.19 (0.43, 3.31)	4	0.53 (0.18, 1.27)	1.50 (0.31, 7.31)
Vaccinated (<60 days), prior infection	94	36 (22, 47)	2	0.46 (0.10, 1.49)	0.41 (0.09, 1.80)	0	Not estimated	Not estimated
Vaccinated (≥60 days), naïve	208	125 (92, 169)	37	1.86 (1.33, 2.53)	1.97 (0.98, 3.96)	13	0.65 (0.37, 1.08)	1.73 (0.50, 6.02)
Vaccinated (≥60 days), prior infection	115	129 (93, 173)	5	0.42 (0.16, 0.93)	0.29 (0.10, 0.80)	2	0.17 (0.04, 0.54)	0.44 (0.08, 2.38)
Bivalent vaccination and prior infection status[h]								
Unvaccinated, naïve	94	-	15	1.36 (0.80, 2.19)	Ref	5	0.45 (0.17, 1.00)	Ref
Vaccinated with no bivalent dose received, naïve	184	120 (72, 167)	36	1.79 (1.27, 2.44)	2.02 (0.98, 4.15)	12	0.60 (0.33, 1.01)	1.51 (0.41, 5.65)
Vaccinated with no bivalent dose received, prior	105	116 (67, 165)	5	0.39 (0.15, 0.85)	0.29 (0.10, 0.79)	2	0.16 (0.03, 0.50)	0.40 (0.07, 2.21)
Vaccinated with at least one bivalent vaccine, naïve	96	58 (34, 89.2)	9	1.24 (0.61, 2.27)	1.05 (0.39, 2.88)	5	0.69 (0.26, 1.51)	2.29 (0.65, 8.09)
Vaccinated with at least one bivalent vaccine, prior	43	60.5 (33.2, 94)	2	0.61 (0.13, 1.95)	0.31 (0.06, 1.62)	0	Not estimated	Not estimated
Time since prior infection[i]								
Naïve[e]	357	98 (54, 150)	68	1.48 (1.16, 1.87)	Ref	28	0.61 (0.41, 0.87)	Ref

≤180 days	129	80 (46, 132)	2	0.20 (0.04, 0.65)	0.12 (0.03, 0.50)	1	0.10 (0.01, 0.47)	0.16 (0.02, 1.17)
>180 days and ≤365 days	218	94 (51, 149)	13	0.60 (0.34, 0.99)	0.35 (0.18, 0.67)	4	0.18 (0.06, 0.44)	0.31 (0.11, 0.87)
>365 days	99	139 (81.2, 190.5)	4	0.50 (0.17, 1.19)	0.29 (0.09, 0.96)	0	Not estimated	Not estimated

Abbreviations: Ref is reference category.

[a]Contributing participants in vaccination categories do not equal the number of participants in the study because participants could contribute to more than one vaccination category since vaccination status is time-varying.

[b]Symptomatic COVID-19 was defined as those with a positive RT-PCR test and at least two COVID-like illness symptoms reported within seven days of the specimen collection date.

[c]All hazard ratios for SARS-CoV-2 infections were adjusted for age, geographic site, underlying health conditions, and race/ethnicity, except the hazard ratio for "Vaccinated, including bivalent dose" which was adjusted for age, underlying health conditions, and race/ethnicity.

[d]All hazard ratios for symptomatic COVID-19 were adjusted for age, underlying health conditions, and race/ethnicity, except the hazard ratio for "Vaccinated, including bivalent dose" which was adjusted for age and underlying health conditions.

[e]No evidence of prior infection.

[f]Prior infection was defined as laboratory-confirmation of infection by RT-PCR from a study-collected specimen, positive anti-N SARS-CoV-2 antibody, or self-report of infection prior to enrollment or September 1, 2022.

[g]Participants completed at least a primary vaccination series (2 doses of Moderna or three doses of Pfizer-BioNTech) and may have also received bivalent doses.

[h]Limited to December 17, 2022, to May 6, 2023, when the bivalent vaccine was available to children 6 month – 4 years of age.

[i]Time since prior infection was calculated as the date of the most recent prior infection to the first week each participant was included in the analysis.