Supplementary Appendix

Supplement to: Lin D-Y, Gu Y, Xu Y, et al. Effects of vaccination and previous infection on omicron infections in children. N Engl J Med. DOI: 10.1056/NEJMc2209371

This appendix has been provided by the authors to give readers additional information about the work.

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Supplementary Methods

Data Collection

We obtained individual-level data on vaccination histories from November 1, 2021 to June 3, 2022 and on clinical outcomes (SARS-CoV-2 infection, hospitalization, death) from March 11, 2020 to June 3, 2022 by linking the North Carolina COVID-19 Surveillance System and COVID-19 Vaccine Management System through a Master Patient Index. We used the 2020 Bridged-Race Population estimates produced by the US Census Bureau to determine the total number of children with each combination of demographic variables (i.e., sex, race/ethnicity, geographic region, and county-level vaccination rate).

COVID-19 case data are populated on the basis of lab reports from clinical laboratories that are mandated to report results. Our dataset contained positive COVID-19 test results for all cases and index reinfections using the unique person identifier and person-event infection variables. COVID-related hospitalization and death are documented through local health department case investigation. For cases reported January 1, 2022 forward, vital records criteria were introduced to expand COVID death surveillance. The definitions of COVID cases and deaths can be found at https://covid19.ncdhhs.gov/dashboard/cases-and-deaths#covid-19-cases-and-deaths.

We used the genetic sequence-based surveillance data produced by the Center for Diseases Control and Prevention: https://covid.cdc.gov/covid-data-tracker/#variant-proportions to divide the study period into three periods of SARS-CoV-2 variants: pre-delta (before July 1, 2021), delta (July 1, 2021 – December 15, 2021), omicron (after December 15, 2021). No individual-level sequence data are available.

Statistical Analysis

Let V_k $(k = 1, \dots, K)$ denote the time when the individual receives the kth type of vaccine (e.g., 1-dose or 2-dose regimen), which is set to infinity if the individual never receives the kth type of vaccine, S_j $(j = 1, \dots, J)$ denote the time of the jth SARS-CoV-2 infection, and X denote demographic variables (i.e., sex, race/ethinicity, geographical region, and county-level vaccination rate). All time variables are measured from the start of the study. In addition, let $N(t)$ denote the number of occurrences for the clinical outcome of interest (e.g., SARS-CoV-2 infection, hospitalization) that the individual has experienced by time t. In the first analysis (Fig. 1A), we specify that the intensity function[1] for $N(t)$ is related to V_k $(k = 1, \dots, K)$, S_j $(j = 1, \dots, J)$, and X in the following form

$$\lambda\left(t \middle| V_1, \dots, V_K, S_1, \dots, S_J, X\right) = \lambda_0(t) \exp\left\{\beta^{\mathrm{T}} X + \sum_{k=1}^{K} \eta_k(t - V_k) I(V_k < t) + \sum_{j=1}^{J} \theta\left(t - S_j\right) I\left(S_j < t\right)\right\}, \quad (1)$$

where $\lambda_0(\cdot)$ is an arbitrary baseline intensity function, β is a set of regression parameters representing the effects of demographic variables, $\eta_k(\cdot)$ is a function characterizing the time-

varying effect of the kth type of vaccine ($k = 1, \dots, K$), $\theta(\cdot)$ is a function characterizing the time-varying effect of a prior infection, and $I(\cdot)$ is the indicator function. Of note, intensity can be interpreted as rate.[2] For $k = 1, \dots, K$, we define the effectiveness of the kth type of vaccine in reducing the rate of the clinical outcome at time t since the first dose by $1 - \exp\{\eta_k(t)\}$. Likewise, we define the effectiveness of prior infection in reducing the rate of the clinical outcome at time t since the prior infection by $1 - \exp\{\theta(t)\}$. To allow the effectiveness of the vaccine and prior infection to depend on the date of vaccination and the type of variant, we allow $\eta_k(\cdot)$ ($k = 1, \dots, K$) to vary accross different vaccination cohorts defined by the date of the first dose, and allow $\theta(\cdot)$ to vary accross different prior infection cohorts defined by the date of prior infection. We estimate all cohort-specific effectiveness under a single model.

In the second analysis (Fig. 1B-1D), we allow the effects of vaccination to potentially differ among previously uninfected versus previously infected individuals, and we also allow the effects of prior infection to potentially differ among unvaccinated versus vaccinated individuals. Specifically, we extend model (1) by incorporating the interactions between vaccination status and prior infection status, such that the linear predictor becomes

$$\begin{aligned}\sum_{k=1}^{K}\{\eta_k(t - V_k)I(V_k < t, V_k \le S_1) + \tilde{\eta}_k(t - V_k)I(S_1 < V_k < t)\} \\ + \sum_{j=1}^{J}\{\theta(t - S_j)I(S_j < t, S_j \le V_{\min}) + \tilde{\theta}(t - S_j)I(V_{\min} < S_j < t)\},\end{aligned} \tag{2}$$

where $V_{\min} = \min(V_1, \dots, V_K)$, $\eta_k(\cdot)$ and $\tilde{\eta}_k(\cdot)$ characterize the time-varying effects of the kth type of vaccine without and with prior infection, respectively ($k = 1, \dots, K$); $\theta(\cdot)$ and $\tilde{\theta}(\cdot)$ characterize the time-varying effects of a prior infection among unvaccinated and vaccinated individuals, respectively. The effectiveness of the vaccine and prior infection is defined accordingly.

In the third analysis (Fig. 1E and 1F), hospitalization caused by SARS-CoV-2 infection is the clinical outcome of interest. Since the number of hospitalizations is small, it is more stable to estimate the effectiveness of the vaccine and prior infection from two separate models. Thus, we exlucde the second summation from model (1) when estimating the effectiveness of the vaccine and exclude the first summation when estimating the effectiveness of prior infection.

For both models (1) and (2), we approximate the time-varying effects by B-splines with degree one (piecewise linear functions), i.e.,

$$\gamma_0 + \gamma_1 t + \gamma_2(t - t_1)_+ + \gamma_3(t - t_2)_+ + \cdots + \gamma_{m+1}(t - t_m)_+, \tag{3}$$

where $t_+ = t$ if $t > 0$ and 0 otherwise, $t_1, t_2, \dots, t_m$ are the m pre-specified change points, and $\gamma_0, \gamma_1, \dots, \gamma_{m+1}$ are the unknown parameters pertaining to the intercept and the slope of each piece. We estimate the parameters by maximizing the partial likelihood.[3] For the effects of vaccination, we remove the intercept γ_0 from (3) since no vaccine takes immediate effect. We consider change points at every 4, 5 or 6 weeks but may omit change points near the end to

improve stability of estimation. For the second analysis (Fig. 1B), we place an additional change point at 3 weeks to impose a common effect until 3 weeks between the 1-dose and 2-dose regimens. We evaluate the performance of the candidate models (i.e., change points at every 4, 5 or 6 weeks) on the basis of the Akaike information criterion (AIC). For the effects of prior infection, we place a change point at two weeks and a second change point in the middle of the follow-up period or one month earlier. We do not place a second change point if the number of events is small (i.e., Fig. 1F). Again, we choose the parametrization with the lowest AIC. The values of AIC for candidate models are shown in Table S7. To minimize the AIC, we place the change points at every 4 weeks for vaccination and place the second change point in the middle of the follow-up period for prior infection.

References

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2. Lin DY, Wei LJ, Yang I, and Ying Z. Semiparametric regression for the mean and ratefunctions of recurrent events. J R Stat Soc B 2000;62:711-30 https://doi.org/10.1111/1467-9868.00259.
3. Lin DY, Gu Y, Wheeler B, et al. Effectiveness of Covid-19 vaccines over a 9-month period in North Carolina. N Engl J Med 2022;386:933-41 https://www.nejm.org/doi/full/10.1056/NEJMoa2117128.

Table S1. Demographic and Clinical Characteristics of the Study Participants.

Characteristic	No. of Children	SARS-CoV-2 Infection		Hospitalization		Death	
	No. and Proportion			*No. and Rate Out of Infections**			
		All	Omicron	All	Omicron	All	Omicron
Total	887,193	193,346	103,338	309 (0.4%)	99 (0.4%)	7 (0.0%)	3 (0.0%)
Vaccination Status							
Unvaccinated	614,036 (69.2%)	174,281 (90.1%)	84,466 (81.7%)	294 (0.5%)	84 (0.5%)	7 (0.0%)	3 (0.0%)
1 dose	37,759 (4.3%)	3,048 (1.6%)	2,924 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2 doses	228,123 (25.7%)	15,986 (8.3%)	15,917 (15.4%)	15 (0.1%)	15 (0.3%)	0 (0.0%)	0 (0.0%)
Booster	7,275 (0.8%)	31 (0.0%)	31 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sex							
Female	434,917 (49.0%)	94,401 (48.8%)	50,269 (48.6%)	145 (0.3%)	40 (0.3%)	2 (0.0%)	1 (0.0%)
Male	452,276 (51.0%)	98,945 (51.2%)	53,069 (51.4%)	164 (0.4%)	59 (0.5%)	5 (0.0%)	2 (0.0%)
Race/Ethnicity							
Black or Hispanic	369,667 (41.7%)	71,728 (37.1%)	36,644 (35.5%)	153 (0.4%)	41 (0.4%)	4 (0.0%)	1 (0.0%)
Other	517,526 (58.3%)	121,618 (62.9%)	66,694 (64.5%)	156 (0.3%)	58 (0.4%)	3 (0.0%)	2 (0.0%)
Geographic Region							
Coastal	250,132 (28.2%)	55,301 (28.6%)	28,337 (27.4%)	83 (0.3%)	30 (0.3%)	0 (0.0%)	0 (0.0%)
Piedmont	557,837 (62.9%)	119,763 (61.9%)	66,112 (64.0%)	189 (0.4%)	57 (0.4%)	6 (0.0%)	3 (0.0%)
Mountain	79,224 (8.9%)	18,282 (9.5%)	8,889 (8.6%)	37 (0.4%)	12 (0.4%)	1 (0.0%)	0 (0.0%)
County-Level Vaccination Rate							
<59%	271,913 (30.6%)	60,331 (31.2%)	28,589 (27.7%)	100 (0.4%)	31 (0.4%)	3 (0.0%)	2 (0.0%)
59–70%	322,178 (36.3%)	69,879 (36.1%)	35,102 (34.0%)	123 (0.4%)	44 (0.4%)	1 (0.0%)	0 (0.0%)
>70%	293,102 (33.0%)	63,136 (32.7%)	39,647 (38.4%)	86 (0.4%)	24 (0.4%)	3 (0.0%)	1 (0.0%)

* The rates of hospitalization and death out of SARS-CoV-2 infections with known hospitalization and survival status are shown in parentheses.

Table S2. Estimates and 95% Confidence Intervals for the Effectiveness of the Two-Dose BNT162b2 Vaccine in Reducing the Rate of SARS-CoV-2 Infection by Date of First Dose, as a Function of Time Elapsed Since the First Dose.*

Weeks	Date of First Dose			
	Nov. 2021	Dec. 2021	Jan. 2022	Feb. – May 2022
1	30.9% (29.3, 32.4)	20.1% (19.0, 21.3)	23.8% (21.6, 26.0)	19.1% (9.8, 27.4)
2	52.2% (50.0, 54.3)	36.2% (34.4, 38.0)	42.0% (38.6, 45.3)	34.5% (18.6, 47.3)
3	67.0% (64.7, 69.1)	49.1% (46.9, 51.2)	55.8% (51.8, 59.5)	47.0% (26.6, 61.7)
4	77.2% (75.0, 79.1)	59.3% (57.0, 61.5)	66.4% (62.2, 70.0)	57.1% (33.8, 72.2)
5	71.6% (69.7, 73.4)	56.2% (54.4, 58.0)	61.1% (57.0, 64.9)	52.4% (34.3, 65.5)
6	64.7% (63.1, 66.2)	52.9% (50.9, 54.8)	55.1% (48.3, 61.0)	47.2% (32.2, 58.8)
7	56.0% (54.9, 57.2)	49.4% (46.4, 52.2)	48.2% (36.5, 57.7)	41.4% (24.6, 54.4)
8	45.3% (44.0, 46.7)	45.5% (41.0, 49.7)	40.1% (21.2, 54.5)	34.9% (9.8, 53.0)
9	41.8% (40.5, 43.2)	43.1% (38.8, 47.1)	38.9% (21.9, 52.2)	34.5% (14.4, 49.9)
10	38.1% (36.8, 39.4)	40.6% (36.4, 44.5)	37.7% (22.5, 49.9)	34.2% (18.0, 47.1)
11	34.1% (32.8, 35.5)	37.9% (33.8, 41.7)	36.4% (23.0, 47.5)	33.8% (20.3, 45.0)
12	29.9% (28.5, 31.3)	35.2% (31.1, 38.9)	35.2% (23.4, 45.1)	33.4% (20.5, 44.2)
13	25.4% (24.0, 26.9)	32.3% (28.3, 36.0)	33.9% (23.6, 42.8)	33.1% (18.6, 45.0)
14	20.7% (19.1, 22.3)	29.2% (25.2, 33.1)	32.5% (23.5, 40.6)	32.7% (14.7, 46.9)
15	15.6% (13.8, 17.3)	26.1% (21.8, 30.1)	31.2% (22.9, 38.6)	32.3% (9.6, 49.3)
16	10.2% (8.2, 12.1)	22.8% (18.2, 27.1)	29.8% (21.7, 37.1)	
17	4.4% (2.2, 6.7)	19.4% (14.3, 24.1)	28.4% (19.7, 36.1)	
18	-1.7% (-4.3, 0.9)	15.8% (10.2, 21.0)	27.0% (17.1, 35.6)	
19	-8.2% (-11.2, -5.3)	12.0% (5.8, 17.8)	25.5% (13.9, 35.5)	
20	-15.1% (-18.5, -11.8)	8.1% (1.0, 14.6)	24.0% (10.2, 35.7)	
21		4.0% (-4.0, 11.4)		
22		-0.3% (-9.3, 8.0)		
23		-4.8% (-15.0, 4.6)		
24		-9.4% (-21.0, 1.0)		

* 95% confidence intervals are given in parentheses.

Table S3. Estimates and 95% Confidence Intervals for the Effectiveness of the Two-Dose BNT162b2 Vaccine in Reducing the Rate of SARS-CoV-2 Infection by Prior Infection Status, as a Function of Time Elapsed Since the First Dose.*

Weeks	Prior Infection	
	No	Yes
1	13.7% (12.8, 14.5)	23.8% (18.6, 28.7)
2	25.5% (24.0, 26.9)	41.9% (33.7, 49.1)
3	35.7% (33.7, 37.6)	55.7% (46.0, 63.7)
4	63.2% (61.0, 65.2)	69.6% (57.4, 78.3)
5	60.1% (58.4, 61.7)	66.8% (57.5, 74.2)
6	56.7% (55.5, 58.0)	63.8% (57.1, 69.5)
7	53.1% (51.9, 54.3)	60.6% (55.1, 65.4)
8	49.2% (47.5, 50.9)	57.0% (49.6, 63.2)
9	43.9% (42.6, 45.3)	53.7% (46.4, 60.0)
10	38.1% (36.7, 39.6)	50.1% (42.9, 56.4)
11	31.7% (29.5, 33.9)	46.3% (39.1, 52.7)
12	24.7% (21.2, 28.0)	42.2% (35.0, 48.7)
13	22.5% (19.5, 25.3)	37.8% (30.3, 44.5)
14	20.2% (16.6, 23.7)	33.1% (25.2, 40.1)
15	17.9% (12.7, 22.8)	27.9% (19.4, 35.5)
16	15.5% (8.1, 22.2)	22.4% (13.0, 30.8)
17	8.6% (1.7, 15.0)	16.5% (5.8, 25.9)
18	1.2% (-5.2, 7.2)	10.1% (-2.2, 20.9)
19	-6.9% (-12.8, -1.3)	3.2% (-11.0, 15.6)
20	-15.6% (-21.0, -10.3)	-4.2% (-20.9, 10.2)
21		-12.1% (-31.7, 4.5)
22		-20.7% (-43.6, -1.5)

* 95% confidence intervals are given in parentheses.

Table S4. Estimates and 95% Confidence Intervals for the Effectiveness of Prior Infection in Reducing the Rate of SARS-CoV-2 Infection by Vaccination Status, as a Function of Time Elapsed Since the Prior Infection.*

Months	Unvaccinated			Vaccinated	
	Pre-delta	Delta	Omicron	Delta	Omicron
1	98.1% (97.1, 98.7)	95.9% (95.1, 96.5)	96.9% (96.2, 97.5)	96.0% (86.3, 98.8)	97.0% (94.8, 98.3)
2	97.1% (95.9, 97.9)	91.8% (90.9, 92.6)	90.7% (89.2, 92.0)	92.6% (82.0, 97.0)	94.3% (91.6, 96.1)
3	95.5% (94.2, 96.6)	83.7% (82.7, 84.6)	71.9% (65.2, 77.3)	86.3% (71.3, 93.5)	89.2% (86.0, 91.6)
4	93.2% (91.7, 94.5)	67.6% (65.8, 69.3)	62.9% (58.8, 66.6)	74.7% (38.7, 89.5)	79.4% (73.8, 83.8)
5	89.8% (88.3, 91.1)	65.1% (63.6, 66.5)	51.0% (39.7, 60.1)	53.1% (-59.2, 86.2)	60.9% (44.6, 72.4)
6	84.5% (83.2, 85.7)	62.4% (60.6, 64.1)			
7	76.5% (74.9, 78.0)	59.5% (56.7, 62.2)			
8	74.5% (73.0, 75.9)	56.4% (52.2, 60.3)			
9	72.4% (71.0, 73.7)	53.1% (47.1, 58.4)			
10	70.1% (68.7, 71.4)				
11	67.6% (66.3, 68.8)				
12	64.8% (63.6, 66.1)				
13	61.9% (60.6, 63.1)				
14	58.7% (57.2, 60.1)				
15	55.2% (53.5, 56.9)				
16	51.5% (49.4, 53.5)				
17	47.4% (44.8, 49.9)				

* 95% confidence intervals are given in parentheses.

Table S5. Estimates and 95% Confidence Intervals for the Effectiveness of the Two-Dose BNT162b2 Vaccine in Reducing the Rate of Hospitalization, as a Function of Time Elapsed Since the First Dose.

Weeks	Estimate (95% CI)
1	41.4% (9.9, 61.9)
2	65.7% (18.8, 85.5)
3	79.9% (26.9, 94.5)
4	88.2% (34.1, 97.9)
5	87.7% (35.0, 97.7)
6	87.1% (35.7, 97.4)
7	86.6% (36.4, 97.2)
8	85.9% (36.9, 96.9)
9	85.3% (37.3, 96.6)
10	84.6% (37.5, 96.2)
11	83.9% (37.6, 95.9)
12	83.2% (37.5, 95.5)
13	82.4% (37.3, 95.1)
14	81.7% (36.8, 94.7)
15	80.8% (36.1, 94.2)
16	80.0% (35.1, 93.8)
17	79.0% (33.8, 93.4)
18	78.1% (32.2, 92.9)
19	77.1% (30.2, 92.5)
20	76.1% (27.8, 92.1)

Table S6. Estimates and 95% Confidence Intervals for the Effectiveness of Prior Infection in Reducing the Rate of Hospitalization, as a Function of Time Elapsed Since the Prior Infection.

Months	Estimate (95% CI)
1	99.5% (73.5, 100.0)
2	99.3% (69.5, 100.0)
3	99.0% (64.8, 100.0)
4	98.5% (59.4, 99.9)
5	97.9% (53.1, 99.9)
6	97.0% (45.7, 99.8)
7	95.6% (37.0, 99.7)
8	93.7% (26.7, 99.5)
9	90.9% (14.5, 99.0)
10	86.9% (-0.4, 98.3)

Table S7. Values of AIC under Candidate Models for Figure 1.

Panel	Model	AIC
A	Every 4 weeks	6128365.4
	Every 5 weeks	6128448.7
	Every 6 weeks	6128671.9
B	Every 4 weeks	6128797.9
	Every 5 weeks	6128899.3
	Every 6 weeks	6129111.7
C & D	Middle of follow-up	6128797.9
	1 month earlier	6128910.6
E	Every 4 weeks	9948.77
	Every 5 weeks	9948.83
	Every 6 weeks	9948.85