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MAJOR ARTICLE

Effectiveness of mRNA Booster Vaccine Against Coronavirus Disease 2019 Infection and Severe Outcomes Among Persons With and Without Immune Dysfunction: A Retrospective Cohort Study of National Electronic Medical Record Data in the United States

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Background. Real-world evidence of coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) booster effectiveness among patients with immune dysfunction are limited.

Methods. We included data from patients in the United States National COVID Cohort Collaborative (N3C) who completed ≥2 doses of mRNA vaccination between 10 December 2020 and 27 May 2022. Immune dysfunction conditions included human immunodeficiency virus infection, solid organ or bone marrow transplant, autoimmune diseases, and cancer. We defined incident COVID-19 BTI as positive results from laboratory tests or diagnostic codes 14 days after at least 2 doses of mRNA vaccination; and severe COVID-19 BTI as hospitalization, invasive cardiopulmonary support, and/or death. We used propensity scores to match boosted versus nonboosted patients and evaluated hazards of incident and severe COVID-19 BTI using Cox regression after matching.

Results. Among patients without immune dysfunction, the relative effectiveness of booster (3 doses) after 6 months from the primary (2 doses) vaccination against BTI ranged from 69% to 81% during the Delta-predominant period and from 33% to 39% during the Omicron-predominant period. Relative effectiveness against BTI was lower among patients with immune dysfunction but remained statistically significant in both periods. Boosted patients had lower risk of COVID-19–related hospitalization (hazard ratios [HR] ranged from 0.5 [95% confidence interval {CI}, .48–.53] to 0.63 [95% CI, .56–.70]), invasive cardiopulmonary support, or death (HRs ranged from 0.46 [95% CI, .41–.52] to 0.63 [95% CI, .50–.79]) during both periods.

Conclusions. Booster vaccines remain effective against severe COVID-19 BTI throughout the Delta- and Omicron-predominant periods, regardless of patients' immune status.

Keywords. COVID-19 vaccination; immune dysfunction; people with HIV; solid organ transplant; real-world evidence.

Vaccines against coronavirus disease 2019 (COVID-19) have demonstrated a high level of effectiveness in preventing infection and death in both clinical trials and real-world settings [1–7]. Before the Omicron variant–related surge [8, 9], the incidence rate of breakthrough infection after primary vaccination was relatively low in both people with and those

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without immune dysfunction [10]. However, a decline over time of antibody response and waning immunity has been observed among individuals following primary vaccination [11, 12]. Therefore, several countries, including Israel [13, 14], the United Kingdom [15], and the United States (US) [16–19], recommended booster vaccination 5–6 months following primary vaccination. Population data have demonstrated that COVID-19 booster doses are effective at preventing severe outcomes and breakthrough infections [13–15, 18–20]. However, booster effectiveness is likely time-varying, given changing dominant strains and waning immunity following primary vaccination.

Another primary evidence gap regarding vaccine effectiveness exists for patients with immune dysfunction since they were largely excluded from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine trials [2, 3]. Large-scale real-world data on the effectiveness of boosters or additional doses among these patients remain scarce. The majority of existing studies including data for patients with immune dysfunction had limited sample size with imprecise effect estimates. Patients with immune dysfunction have a higher rate and risk of breakthrough infection after primary vaccination [10]. Based largely on improved immunogenicity following the third dose of messenger RNA (mRNA) vaccine among solid organ transplant (SOT) recipients [21], Centers for Disease Control and Prevention (CDC) guidelines suggest a third vaccine dose as primary vaccination for patients with severe immune dysfunction [16]. This further increases the complexity of evaluating booster vaccine effectiveness in this vulnerable population. Moreover, patients with immune dysfunction encompass a diverse array of patients affected by conditions spanning from SOT, human immunodeficiency virus (HIV) infection, and autoimmune diseases, to cancer. Whether improved immunogenicity translates to population-level effectiveness among patients with diverse immune dysfunction conditions remains unclear. We determined booster vaccine effectiveness following COVID-19 mRNA vaccination among persons with and without immune dysfunction, including data from the Delta and Omicron variant–predominant periods in a national sample of US patients.

METHODS

Setting, Design, and Study Sample

We conducted a retrospective cohort study utilizing individual-level data from the National COVID Cohort Collaborative (N3C), a secure and centralized electronic medical record (EMR)–based data repository of COVID-19 testing, diagnoses, and vaccination from large academic medical centers across the US initiated by the National Center for Advancing Translational Science (NCATS). Detailed study design, data collection, sampling approach, and data harmonization have been described previously [10, 22, 23] and are summarized in the Supplementary Methods. In brief, each study site provides demographic, medication, laboratory, diagnoses, and vital status data to the central data repository, which is harmonized into the Observational Medical Outcomes Partnership data model. This retrospective cohort study received institutional review board (IRB) approval under the authority of the National Institutes of Health IRB (IRB00249128) with the Johns Hopkins University School of Medicine as a central IRB (IRB00309494). The limited datasets are shared through the NCATS Data Enclave under a data-sharing agreement. Data access for the current study was approved by the N3C Data Access Committee.

The analytical sample for the current study included N3C patients who (1) completed primary COVID-19 mRNA vaccination (defined below) between 10 December 2020 to the end of the study observation period of 27 May 2022 in the N3C Enclave, and (2) from study sites that passed initial quality checks (Supplementary Figure 1). We used 10 December 2020, the date the US Food and Drug Administration (FDA) granted emergency use authorization to the first COVID-19 vaccine [24], as the beginning of our observation period. Details on the latest date each study site reported their data are presented in Supplementary Figure 2.

Patient Consent Statement

No informed consent was obtained because the study used a limited dataset.

SARS-CoV-2 Vaccination

Supplementary Table 1 provides details on all key concept definitions. Our dataset included the 2 SARS-CoV-2 mRNA vaccines (Pfizer-BioNTech [BNT162b2] and Moderna [mRNA-1273]) currently approved or authorized by the FDA. We categorized primary vaccination as completion of 2 doses for the mRNA vaccines in the primary analyses. Booster vaccine was defined as an additional dose of mRNA vaccine following the primary vaccines. The recommendations for severely immunocompromised (ISC) patients (defined below) have evolved over time throughout the pandemic, from using the same recommendations as the general population early in the pandemic (2 doses of vaccine as primary series), to including an additional dose (3 doses of mRNA vaccine) as their primary series later in the pandemic [25]. To reflect these changes, we assessed the booster effectiveness among patients with severe ISC conditions in 2 ways: (1) comparing third dose versus second dose of mRNA vaccine and (2) comparing fourth dose versus third dose of mRNA vaccine.

COVID-19 Case Definition and Outcomes

COVID-19 breakthrough infections were defined as patients with positive results from real-time polymerase chain reaction,

antigen test, and diagnostic codes [22, 23, 26, 27]. To allow for an immune response, vaccine breakthrough infection was defined as a COVID-19 diagnosis ≥14 days following vaccination after primary or booster vaccination. We defined COVID-19–related hospitalization and invasive ventilation based on EMR classification procedures and conditions (Supplementary Table 1). Death was identified based on date of death. All encounters or outcomes ≤45 days following a COVID-19 breakthrough infection were considered COVID-19 related.

Preexisting Conditions and Covariates

Demographics (age, sex, and race/ethnicity) and diagnoses of preexisting conditions (immune dysfunction and other comorbid conditions, Supplementary Table 1) were identified from 1 January 2018 until either the date of breakthrough infection or 27 May 2022 (nonbreakthrough cases). Immune dysfunction conditions included HIV infection, solid organ or bone marrow transplant, autoimmune and rheumatologic diseases, and cancer. Further refinement to identify patients with moderate or severe immune dysfunction were based on CDC recommendations [28] (Supplementary Methods 1 and 5), and included history of leukemia or lymphoma, receipt of a solid organ or bone marrow transplant, people with HIV with CD4 count <350 cells/μL or viral load >50 copies/mL, and patients with rheumatologic diseases on active immunosuppressive therapy. The distribution of patients with and without immune dysfunction by each site is presented in Supplementary Methods 4. The number of comorbidities (including severe heart disease, peripheral vascular disease, stroke, dementia, pulmonary diseases, liver disease, diabetes mellitus, renal diseases, and cancer) was classified as 0, 1, 2, or ≥3. Geographic regions were defined based on residential ZIP (postal) codes and classified into: Northeast, Midwest, West, South, and unknown based on infection rates and sampling density (Supplementary Figure 3).

Statistical Analysis

To account for waning or residual immunity from primary vaccination or natural infection, date of vaccination, and differences in patient characteristics, at each month following primary vaccination, we created comparable cohorts of patients who received boosters (boosted group) propensity score matched to those who did not receive boosters (nonboosted group). Propensity scores were estimated based on demographics, comorbidities, geographic region, prior COVID-19 infection, time between prior COVID-19 infection and primary vaccination, and calendar month of primary vaccination. Successful match was indicated by standardized mean differences <0.1 for each variable and total distance between boosted and matched nonboosted groups (Supplementary Figures 4 and 5). We identified the time interval between primary vaccine and booster dose in the boosted patients and assigned the same interval to the matched nonboosted patients as the beginning of person-time of follow-up. Person-time of follow-up ends on the earliest date of breakthrough infection or censoring (death, end of data reporting for each site [Supplementary Figure 2], or 27 May 2022). We used Cox regression models to compare 120-day hazards of breakthrough infection, hospitalization, or severe outcomes (invasive ventilation or death) in the propensity score–matched boosted versus nonboosted group. Relative effectiveness comparing boosted versus nonboosted groups was calculated based on (1 – hazard ratio [HR]) × 100% [29]. We stratified analyses by time interval since full vaccination (2 doses of mRNA vaccine), severity of immune dysfunction, and by Delta-predominant (20 June 2021 to 19 December 2021) or Omicron-predominant (20 December 2021 to 27 May 2022) periods based on CDC reporting [9]. We conducted further analyses among patients with moderate to severe immune dysfunction to assess the relative effectiveness of fourth dose versus third dose of mRNA vaccine during Delta- and Omicron-predominant periods using logistic regression models to control for the same covariates aforementioned in the propensity score matching.

We conducted sensitivity analyses to include all COVID-19 infections after the last dose of vaccination (irrespective of the 14-day lag period) in defining breakthrough infection. All data management and analyses were conducted in the N3C Data Enclave using Python and Spark R.

RESULTS

Patient Characteristics

Among 2 199 464 patients from 27 sites that had completed 2 or more doses of mRNA vaccination, 949 457 (43.2%) received a booster vaccine (median interval between primary vaccine to booster dose: 7.7 months [interquartile range {IQR}, 6.9–8.5 months]). At completion of 2 doses of mRNA vaccine, the median age was 49 years (IQR, 32–64 years); 60% of patients were female, 61% non-Hispanic White, 12% non-Hispanic Black, 13% Hispanic, and 3.4% Asian American/Pacific Islander (Table 1). We identified 385 167 (17.5%) patients with an immune dysfunction diagnosis, and 2.1% are defined as moderate to severe immune dysfunction. Among patients with immune dysfunction, more than two-thirds had either cancer or rheumatologic disease. More than 90% of all participants completed 2 doses of mRNA vaccine before 24 September 2021 when booster vaccines were initially recommended for high-risk populations [16].

Overall Booster Vaccination and Breakthrough Infection

Figure 1 demonstrates weekly figures for number of primary vaccinations completed or booster doses given and number of breakthrough infections by booster status. The notable Omicron uptick is clearly identifiable. Overall breakthrough infections were low with 106 878 (5.7%) infections in the

Table 1. Characteristics of Patients Completing at Least 2 Doses of Coronavirus Disease 2019 Messenger RNA Vaccine in the National COVID Cohort Collaborative Cohort, 10 December 2020 to 27 May 2022

Variable[a]	Overall Cohort (N = 2 199 464)	Immune Status[b]			Vaccine Status	
		Patients Without Immune Dysfunction (n = 1 814 297)	Patients With Mild Immune Dysfunction (n = 339 453)	Patients With Moderate/Severe Immune Dysfunction (n = 45 714)	Primary Vaccination (n = 1 250 007)	Primary Vaccination With Booster[c] (n = 949 457)
Age, y, median (IQR)	49 (32–64)	45 (30–61)	65 (53–74)	63 (51–72)	44 (28–60)	56 (39–68)
Female sex	1 317 101 (60)	1 107 220 (61)	189 365 (56)	20 516 (45)	747 882 (60)	569 219 (60)
Race and ethnicity						
Non-Hispanic White	1 338 626 (61)	1 073 050 (59)	235 981 (70)	29 595 (65)	725 075 (58)	613 551 (65)
Non-Hispanic Black	256 574 (12)	205 898 (11)	43 351 (13)	7325 (16)	150 303 (12)	106 271 (11)
Hispanic	287 291 (13)	256 903 (14)	26 068 (7.7)	4320 (9.5)	184 221 (15)	103 070 (11)
Asian American/Pacific Islander	73 778 (3.4)	65 077 (3.6)	7659 (2.3)	1042 (2.3)	36 167 (2.9)	37 611 (4.0)
Other	243 195 (11)	213 369 (12)	26 394 (7.8)	3432 (7.5)	154 241 (12)	88 954 (9.4)
No. of comorbidities[d]						
0	1 286 608 (58)	1 221 238 (67)	63 522 (19)	1848 (4.0)	792 473 (63)	494 135 (52)
1	448 720 (20)	344 981 (19)	94 073 (28)	9666 (21)	234 600 (19)	214 120 (23)
2	198 933 (9.0)	119 359 (6.6)	69 142 (20)	10 432 (23)	93 206 (7.5)	105 727 (11)
≥3	265 203 (12)	128 719 (7.1)	112 716 (33)	23 768 (52)	129 728 (10)	135 475 (14)
Vaccine manufacturer						
Pfizer/BioNTech	1 501 502 (68)	1 251 780 (69)	219 559 (65)	30 163 (66)	885 786 (71)	615 716 (65)
Moderna	697 962 (32)	562 517 (31)	119 894 (35)	15 551 (34)	364 221 (29)	333 741 (35)
Date of primary vaccination (completed 2 doses of mRNA vaccine)						
10 Dec 2020–28 Feb 2021	487 079 (22)	378 934 (21)	98 022 (29)	10 123 (22)	198 311 (16)	288 768 (30)
1 Mar 2021–19 Jun 2021	1 295 995 (59)	1 061 691 (59)	205 493 (61)	28 811 (63)	673 491 (54)	622 504 (66)
20 Jun 2021–24 Sep 2021	234 163 (11)	210 408 (12)	20 202 (6.0)	3553 (7.8)	200 191 (16)	33 972 (3.6)
25 Sep 2021–20 Dec 2021	125 327 (5.7)	113 269 (6.2)	10 231 (3.0)	1827 (4.0)	121 509 (9.7)	3818 (0.4)
21 Dec 2021–27 May 2022	56 900 (2.6)	49 995 (2.8)	5505 (1.6)	1400 (3.1)	56 505 (4.5)	395 (<0.1)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; mRNA, messenger RNA.

[a]Variables are reported at the time of primary vaccination.

[b]Patients with immune dysfunction included persons with human immunodeficiency virus infection (4.5%), autoimmune rheumatologic diseases (26%), solid organ transplant (2.4%), multiple sclerosis (1.5%), bone marrow transplant (<1%), and cancer (43%); 23% had ≥2 conditions and 13% were considered to have moderate to severe immune dysfunction (defined in Supplementary Methods 1 and 5).

[c]Primary vaccination indicated 2 doses of mRNA vaccine. Booster vaccination indicated 3 doses of mRNA vaccine.

[d]Comorbidities include severe heart disease, peripheral vascular disease, stroke, dementia, pulmonary diseases, liver disease, diabetes mellitus, renal diseases, and cancer.

Delta-predominant period and notably higher with 321 033 (14.4%) infections during the Omicron-predominant period.

Booster Effectiveness in Patients Without Immune Dysfunction

Among patients without immune dysfunction, 3 doses of mRNA vaccine were highly effective against breakthrough infection after 6 months following primary vaccination (2 doses) during the Delta period, ranging from 69% to 81% (HRs ranged from 0.31 [95% confidence interval [CI], .26–.36] to 0.19 [95% CI, .18–.21]; Table 2) with notably lower effectiveness observed during the Omicron period, ranging from 33% to 39% protection (HRs ranged from 0.67 [95% CI, .63–.71] to 0.61 [95% CI, .60–.62]; Table 2). The relative effectiveness was reported in range based on the time of booster vaccine since the primary vaccination (Table 2).

Receiving a booster vaccine significantly reduced the risk of COVID-19 adverse outcomes (hospitalization, invasive ventilation, death) in both the Delta and Omicron periods (Figure 2*A* and 2*B*, Supplementary Tables 2 and 3). Risk reduction for hospitalization and severe outcomes (invasive ventilation use/death) in propensity score–matched models decreased from 79% (HR, 0.21 [95% CI, .19–.22]) and 90% (HR, 0.10 [95% CI, .08–.13]), respectively, during the Delta period, to 43% (HR, 0.57 [95% CI, .55–.58]) and 54% (HR, 0.46 [95% CI, .41–.52]), respectively, during the Omicron period (Figure 2*A* and 2*B*).

Booster Effectiveness in Patients With Immune Dysfunction

The relative effectiveness against breakthrough infection comparing 3 doses versus 2 doses of mRNA vaccine was similar in patients with mild immune dysfunction and patients without immune dysfunction during both the Delta and Omicron periods (Table 2). The effectiveness of 3 doses versus 2 doses of vaccine against breakthrough infection was moderately effective among patients with severe immune dysfunction during the

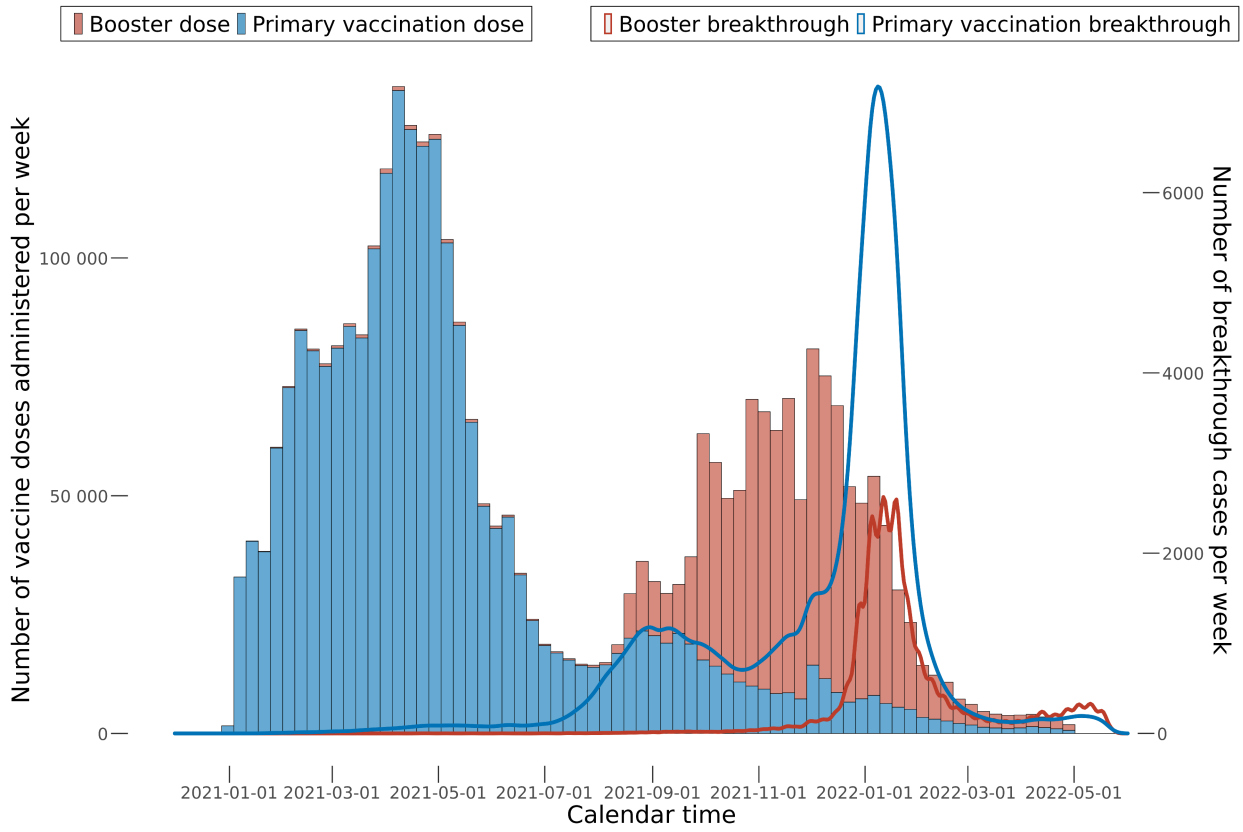

Figure 1. Coronavirus disease 2019 vaccination uptake and breakthrough infections by booster receipt status in the National COVID Cohort Collaborative, 10 December 2021 to 27 May 2022. Primary vaccination indicates 2 doses of messenger RNA (mRNA) vaccine. Booster vaccination indicates 3 doses of mRNA vaccine.

Delta period (ranged from 42% to 77%), but was further reduced during the Omicron period (4% to 25%) (Table 2).

Despite reduced protection against breakthrough infection, boosters remain protective against more severe outcomes including COVID-19–related hospitalization, ventilation, and death. Receipt of 3 doses of mRNA vaccine was associated with >75% reduction in hospitalization and severe outcomes among patients with both mild and moderate-to-severe immune dysfunction during the Delta-predominant period (Figure 2*A*, Supplementary Table 2). During the Omicron-predominant period, relative effectiveness against adverse outcomes was reduced to 50% and 54% in hospitalization and severe outcomes among patients with mild immune dysfunction, and further reduced to 37% and 37% among patients with moderate to severe immune dysfunction (Figure 2*B*, Supplementary Table 3). Among patients with moderate to severe immune dysfunction, predicted prevalence of severe outcomes for the boosted and nonboosted group during Omicron were 8.1 and 13 per 1000 persons, respectively, which were 12 and 8 times as high as patients without immune dysfunction (0.7 and 1.6 per 1000 persons, respectively, Supplementary Table 3).

Patients who received a booster vaccine soon (≤5 months) following primary vaccination likely represent a high-risk group that required an additional dose of vaccine to increase immune response based on clinical decisions. Therefore, estimates within this group may represent potential indication bias, despite our effort of propensity score matching. Results from this group were reported in Supplementary Table 4 and were consistent with the observation in the primary analyses (Table 2) with reduced effect size.

Four Doses Versus 3 Doses of mRNA Vaccine Effectiveness Among Patients With Moderate/Severe Immune Dysfunction

Among patients with moderate/severe immune dysfunction, 26 379 received 3 doses of mRNA vaccine and 4299 received 4 doses of mRNA vaccine. Four doses of mRNA vaccine significantly reduced risk of breakthrough infection and adverse outcomes among patients with moderate to severe immune dysfunction (Table 3). Specifically, the odds of breakthrough, hospitalization, and severe outcomes were reduced by 92% (adjusted odds ratio [aOR], 0.08 [95% CI, .04–.14]), 97% (aOR, 0.03 [95% CI, .01–.12]), and 95% (aOR, 0.05 [95% CI, .01–.36]) during the Delta period, respectively. The risk reduction of 4 doses versus 3 doses of mRNA vaccine was somewhat lower during the Omicron compared to Delta period, but remained highly significant (aORs for breakthrough infection, hospitalization, and severe outcomes were 0.14 [95% CI,

Table 2. Coronavirus Disease 2019 Booster Vaccine Effectiveness by Timing of Receipt Following 2 Doses of Messenger RNA Vaccine Among Patients With and Without Immune Dysfunction

Variant-Predominant Period	Month[a]	Breakthrough Events During Follow-up		Sample Size in Each Group (Boosted or Nonboosted)[b]	Predicted Cumulative Prevalence of BTI by 120 Days, Per 1000 Persons (95% CI)		Booster[c] Effectiveness,[d] % (95% CI)	HR (95% CI)	*P* Value
		Boosted Group	Nonboosted Group		Boosted Group	Nonboosted Group			
Patients without immune dysfunction									
Delta-predominant period (20 Jun act2021 to 19 Dec 2021)	6	156	403	12 869	27 (22–32)	88 (74–101)	69 (64–74)	0.31 (.26–.36)	<.01
	7	787	3261	119 817	24 (19–30)	122 (95–149)	80 (78–82)	0.20 (.18–.21)	<.01
	8	1018	4253	168 528	31 (17–45)	158 (87–230)	81 (79–82)	0.19 (.18–.21)	<.01
	9	855	3116	115 749	23 (19–27)	101 (84–118)	78 (79–76)	0.22 (.21–.24)	<.01
Omicron-predominant period (20 Dec 2021 to 27 May 2022)	6	1308	1718	19 634	86 (80–91)	128 (129–136)	33 (29–37)	0.67 (.63–.71)	<.01
	7	13 744	17 583	135 925	116 (113–118)	176 (173–179)	34 (33–35)	0.66 (.65–.67)	<.01
	8	19 392	27 437	207 307	106 (105–108)	174 (172–177)	39 (38–40)	0.61 (.60–.62)	<.01
	9	15 794	22 584	169 574	105 (103–106)	169 (166–171)	38 (37–39)	0.62 (.61–.63)	<.01
Patients with mild immune dysfunction									
Delta-predominant period (20 Jun 2021 to 19 Dec 2021)	6	130	311	9231	21 (17–25)	69 (59–80)	70 (63–75)	0.30 (.25–.37)	<.01
	7	337	969	36 559	26 (19–32)	99 (75–124)	74 (71–77)	0.26 (.23–.29)	<.01
	8	336	1173	49 120	19 (16–23)	86 (72–100)	77 (75–80)	0.23 (.20–.25)	<.01
	9	181	613	31 116	16 (13–18)	62 (53–71)	75 (71–79)	0.25 (.21–.29)	<.01
Omicron-predominant period (20 Dec 2021 to 27 May 2022)	6	553	714	9846	93 (81–105)	136 (119–154)	32 (24–39)	0.68 (.61–.76)	<.01
	7	2692	3342	37 667	90 (86–95)	131 (125–137)	31 (28–34)	0.69 (.66–.72)	<.01
	8	3850	4910	51 696	88 (85–92)	129 (124–133)	31 (29–34)	0.69 (.66–.71)	<.01
	9	2731	4013	37 845	82 (79–85)	136 (131–140)	40 (37–42)	0.60 (.58–.63)	<.01
Patients with moderate/severe immune dysfunction									
Delta-predominant period (20 Jun 2021 to 19 Dec 2021)	6	142	170	3760	57 (46–68)	97 (78–116)	42 (28–53)	0.58 (.47–.72)	<.01
	7	132	200	5367	61 (39–83)	128 (83–174)	52 (41–61)	0.48 (.39–.59)	<.01
	8	79	145	4317	81 (41–121)	190 (98–281)	57 (44–67)	0.43 (.33–.56)	<.01
	9	≤20	55	2341	22 (5–39)	98 (34–161)	77 (60–87)	0.23 (.13–.40)	<.01
Omicron-predominant period (20 Dec 2021 to 27 May 2022)	6	282	277	3620	134 (117–151)	139 (121–157)	4 (<0–18)	0.96 (.82–1.13)	.66
	7	488	535	5319	137 (122–151)	166 (149–184)	18 (7–27)	0.82 (.73–.93)	<.01
	8	468	544	4507	133 (119–148)	178 (159–196)	25 (16–33)	0.75 (.67–.84)	<.01
	9	344	373	3003	132 (118–146)	159 (142–176)	17 (5–28)	0.83 (.72–.95)	<.01

All statistical tests were 2-sided.

Abbreviations: BTI, breakthrough infection; CI, confidence interval; HR, hazard ratio.

[a]Month indicates month since full vaccination. Immune dysfunction includes people with human immunodeficiency virus infection, solid organ or bone marrow transplant, autoimmune diseases, and cancer.

[b]Boosted and nonboosted groups were 1:1 propensity score matched every month after full vaccination by demographics, geographic region, comorbidities, prior coronavirus disease 2019, and time of full vaccination. Cells with ≤20 persons were collapsed per National COVID Cohort Collaborative requirements. No result that can be back-calculated to related cell is allowed to be reported.

[c]Primary vaccination indicates 2 doses of messenger RNA (mRNA) vaccine. Booster vaccination indicates 3 doses of mRNA vaccine.

[d]Booster effectiveness was calculated as (1 – HR) × 1.

.09–.20], 0.16 [95% CI, .09–.27], and 0.10 [95% CI, .03–.32], respectively).

Sensitivity Analyses

Results from sensitivity analyses include all COVID-19 infections after the last dose of vaccination (irrespective of the 14-day lag period) in defining breakthrough infection (Supplementary Tables 5 and 6) and were highly consistent with those from the primary analysis.

DISCUSSION

Using data from a nationally sampled cohort of >2 million US patients who had completed at least 2 doses of mRNA vaccination against COVID-19, our study provides among the strongest real-world evidence to date defining the protection afforded by booster doses in preventing infection, hospitalization, and death among patients with and without immune dysfunction. Our data are a representative sample of the geographic, racial, and ethnic diversity of the US, and our

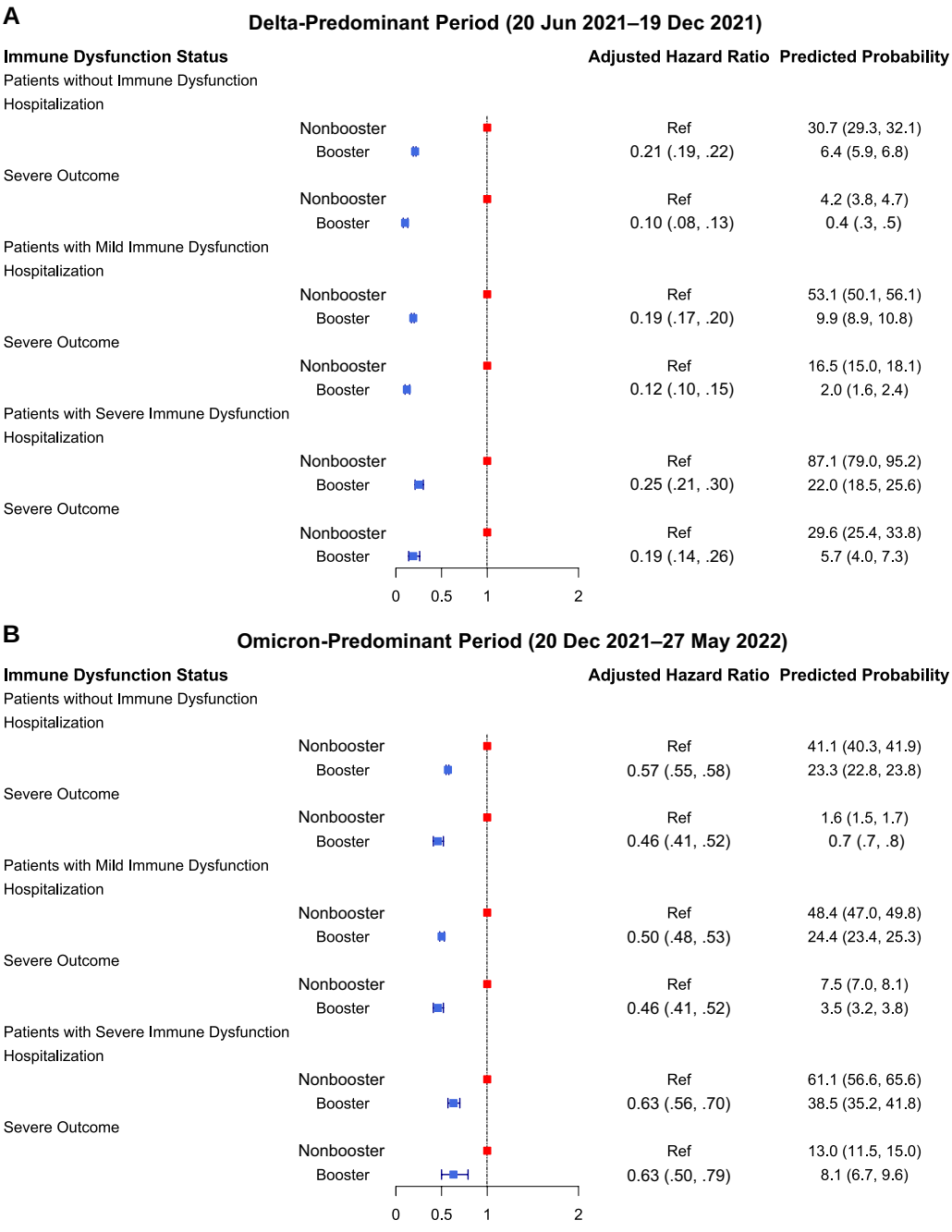

Figure 2. Risk of coronavirus disease 2019 (COVID-19) adverse outcomes by booster vaccine status among patients with and without immune dysfunction during time periods of Delta and Omicron variant predominance in the United States. *A*, Delta-predominant period (20 June 2021–19 December 2021). *B*, Omicron-predominant period (20 December 2021–27 May 2022). Models were adjusted for demographics, geographic region, comorbidities, prior COVID-19, and calendar time of primary vaccination. All statistical tests were 2-sided. Primary vaccination indicates 2 doses of messenger RNA (mRNA) vaccine. Booster vaccination indicates 3 doses of mRNA vaccine. Values in parentheses indicate 95% confidence intervals.

findings are likely to be generalizable across the US population. In patients without immune dysfunction, booster effectiveness in preventing breakthrough infection was notably high during the Delta period, although effectiveness declined to <40% during the Omicron period. Comparing boosted to nonboosted persons, booster vaccine was highly effective against COVID-19–related hospitalization, ventilation, or death, although protection waned somewhat during the Omicron period. Notably, the likelihood of severe outcomes among the nonboosted group during the Delta period was substantially higher than during the Omicron period, consistent with reduced virulence of Omicron compared to the Delta variant.

Table 3. Four Doses Compared to 3 Doses of Messenger RNA Vaccine Effectiveness Against Coronavirus Disease 2019 Breakthrough Infection and Severe Outcomes Among Patients With Severe Immune Dysfunction in the United States

		4-Dose Group		3-Dose Group			
Variant-Specific Period	Outcomes	Event	No Event	Event	No Event	Adjusted OR[a] (95% CI)	*P* Value
Delta (20 Jun 2021 to 19 Dec 2021)	BTI	<20	4288	418	21 662	0.08 (.04–.14)	<.01
	Hospitalization	<20	4297	174	21 906	0.03 (.01–.12)	<.01
	Ventilation/death	<20	4293	172	21 798	0.05 (.01–.36)	<.01
Omicron (20 Dec 2021 to 27 May 2022)	BTI	27	4246	1527	20 021	0.14 (.09–.20)	<.01
	Hospitalization	<20	4272	798	21 000	0.16 (.09–.27)	<.01
	Ventilation/death	<20	4296	99	21 981	0.10 (.03–.32)	<.01

Abbreviations: BTI, breakthrough infection; CI, confidence interval; OR, odds ratio.

[a]Adjusted ORs controlled for demographics, geographic region, comorbidities, prior coronavirus disease 2019 infection, and time of full vaccination.

Among patients with moderate to severe immune dysfunction, the third dose of mRNA vaccine offered significant protection against severe outcomes (hospitalization, use of ventilation, and death), although the protection was moderate to low against breakthrough infection. An additional booster dose (fourth dose of mRNA vaccine) substantially increased protection against breakthrough infection and adverse outcomes in both Delta and Omicron periods among persons with immune dysfunction. Collectively, additional doses of vaccine provided continued protection against breakthrough infection and adverse outcomes even during the Omicron-predominant period, regardless of patients' immune status.

Persons with severe immune dysfunction diagnoses have been recognized to both respond less well to vaccination and also to have more serious consequences from COVID-19 [10, 30–32]. We confirmed that persons with severe immune dysfunction demonstrated notably lower protection against breakthrough infection from the third dose of mRNA vaccination than the general population during the Delta-predominant period, and protection was further reduced during the Omicron-predominant period. However, the fourth dose of mRNA vaccine offered substantially higher protection against breakthrough infection and adverse outcomes, supporting the CDC recommendation [16, 28] of additional dose of vaccination or annual vaccination in this vulnerable population. Patients with severe immune dysfunction, irrespective of booster status, were highly vulnerable, with 8-fold higher likelihood of severe COVID-19 disease compared to patients without immune dysfunction. These results highlight the importance of staying up to date with vaccine recommendations and support the recommendations for routinely updated vaccination (such as annually) to protect patients with immune dysfunction.

Consistent with studies conducted before the Omicron-predominant period [13, 14], our study showed that booster effectiveness against breakthrough infection was high during the Delta-predominant period, but had reduced effectiveness during Omicron, although it remained effective against severe outcomes in the general population [15, 19, 20]. Data from the VISION cohort also suggested booster effectiveness reduced over the Omicron period [19]. Our study provided further real-world data including the large US national sample of study participants from 50 states and the District of Columbia and one of the largest samples to date to demonstrate booster vaccine effectiveness during different variant-predominant periods.

Our study has certain limitations. First, we relied on EMR data primarily from large academic medical centers to capture COVID-19 vaccination status, and we may not fully capture vaccination outside of hospital settings in all sites. We conducted thorough and rigorous evaluation of data quality at each study site and only included sites with the highest quality of vaccination data. The booster vaccination rate reported in our study (>40%) is comparable to the national estimates by the CDC [33]. Despite these efforts, the misclassification of vaccination could lead to an underestimate of booster effectiveness. Albeit potentially underestimating effectiveness, we still observed booster vaccines were effective among patients with and without immune dysfunction, so our conclusions are not likely to change. Second, given that many breakthrough infections are asymptomatic to mild, and the use of COVID-19 home testing substantively increased during this time, the prevalence of breakthrough infection is likely underestimated. However, the hospital-based EMR nature of N3C will be less likely to miss adverse events (hospitalization and severe COVID-19 cases). Third, antivirals, monoclonal antibodies, or immunomodulatory therapies as preemptive therapies to ameliorate COVID-19 progression were available among high-risk and hospitalized patients during the Delta and Omicron periods. The protective effects of these therapeutics against COVID-19 may result in overestimates of the effect of vaccination on severe outcomes in some patients.

In summary, by leveraging national representative medical records data with the intense matching of boosted and nonboosted patients, we demonstrated that booster doses of vaccine were highly effective against COVID-19 breakthrough infection and adverse outcomes during the Delta-predominant period but offered reduced protection during the Omicron-predominant

period. Compared to 2 doses of mRNA vaccination, third dose of vaccine only offered minimal further protection among patients with moderate/severe immune dysfunction during the Omicron-predominant period. However, the fourth dose of mRNA vaccine substantially increased protection within this vulnerable population. While COVID-19 cases and deaths are receding, continued vigilance and annual or periodic vaccine administration will both complement and reduce the need for therapeutics among highly vulnerable persons with immune dysfunction.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Data availability. All data were collected through the NCATS N3C Data Enclave, which represents one of the largest, most secure clinical data resources for accelerating research on COVID-19. Details on data collection and harmonization are presented in Supplementary Methods 1–5. It also includes a powerful analytics platform and tool set for online discovery, visualization, and collaboration using PySpark built on Palantir's Foundry platform. Investigators can request access to the N3C Enclave here: https://ncats.nih.gov/n3c/about/applying-for-access. All concept sets in use are available in the N3C Knowledge Store. All data management and analyses were conducted in the N3C Data Enclave using Python and Spark R. Data analysis code can be made available in GitHub upon request.

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APPENDIX

N3C attribution

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Institutional review board

The N3C data transfer to NCATS is performed under a Johns Hopkins University Reliance Protocol #IRB00249128 or individual site agreements with the National Institutes of Health (NIH). The N3C Data Enclave is managed under the authority of the NIH; information can be found at https://ncats.nih.gov/n3c/resources.

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