Association of COVID-19 Vaccination With Symptomatic SARS-CoV-2 Infection by Time Since Vaccination and Delta Variant Predominance

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IMPORTANCE Monitoring COVID-19 vaccine performance over time since vaccination and against emerging variants informs control measures and vaccine policies.

OBJECTIVE To estimate the associations between symptomatic SARS-CoV-2 infection and receipt of BNT162b2, mRNA-1273, and Ad26.COV2.S by day since vaccination before and during Delta variant predominance (pre-Delta period: March 13-May 29, 2021; Delta period: July 18-October 17, 2021).

DESIGN, SETTING, AND PARTICIPANTS Test-negative, case-control design with data from 6884 US COVID-19 testing sites in the pharmacy-based Increasing Community Access to Testing platform. This study included 1634 271 laboratory-based SARS-CoV-2 nucleic acid amplification tests (NAATs) from adults 20 years and older and 180 112 NAATs from adolescents 12 to 19 years old with COVID-19–like illness from March 13 to October 17, 2021.

EXPOSURES COVID-19 vaccination (1 Ad26.COV2.S dose or 2 mRNA doses) 14 or more days prior.

MAIN OUTCOMES AND MEASURES Association between symptomatic infection and prior vaccination measured using the odds ratio (OR) from spline-based multivariable logistic regression.

RESULTS The analysis included 390 762 test-positive cases (21.5%) and 1 423 621 test-negative controls (78.5%) (59.9% were 20-44 years old; 9.9% were 12-19 years old; 58.9% were female; 71.8% were White). Among adults 20 years and older, the BNT162b2 mean OR for days 14 to 60 after a second dose (initial OR) was lower during the pre-Delta period (0.10 [95% CI, 0.09-0.11]) than during the Delta period (0.16 [95% CI, 0.16-0.17]) and increased with time since vaccination (per-month change in OR, pre-Delta: 0.04 [95% CI, 0.02-0.05]; Delta: 0.03 [95% CI, 0.02-0.03]). The initial mRNA-1273 OR was 0.05 (95% CI, 0.04-0.05) during the pre-Delta period, 0.10 (95% CI, 0.10-0.11) during the Delta period, and increased with time (per-month change in OR, pre-Delta: 0.02 [95% CI, 0.005-0.03]; Delta: 0.03 [95% CI, 0.03-0.04]). The Ad26.COV2.S initial OR was 0.42 (95% CI, 0.37-0.47) during the pre-Delta period and 0.62 (95% CI, 0.58-0.65) during the Delta period and did not significantly increase with time since vaccination. Among adolescents, the BNT162b2 initial OR during the Delta period was 0.06 (95% CI, 0.05-0.06) among 12- to 15-year-olds, increasing by 0.02 (95% CI, 0.01-0.03) per month, and 0.10 (95% CI, 0.09-0.11) among 16- to 19-year-olds, increasing by 0.04 (95% CI, 0.03-0.06) per month.

CONCLUSIONS AND RELEVANCE Among adults, the OR for the association between symptomatic SARS-CoV-2 infection and COVID-19 vaccination (as an estimate of vaccine effectiveness) was higher during Delta variant predominance, suggesting lower protection. For mRNA vaccination, the steady increase in OR by month since vaccination was consistent with attenuation of estimated effectiveness over time; attenuation related to time was greater than that related to variant.
Randomized clinical trials of COVID-19 vaccines authorized or approved for use in the US reported high efficacy against symptomatic disease in adults: 95% for BNT162b2 (Pfizer-BioNTech), 1 94% for mRNA-1273 (Moderna), and 67% for Ad26.COV2.S (Janssen/Johnson & Johnson). Early observational studies reported similarly high protection. However, subsequent studies indicated that protection from mRNA vaccines (BNT162b2 and mRNA-1273) against infection may decrease with time since vaccination and appeared to be lower against the SARS-CoV-2 Delta (B.1.617.2) variant, which was the dominant variant in the US from mid-July until late December 2021.11 Because of the timing of COVID-19 vaccine introduction, distinguishing effects of the Delta variant on vaccine effectiveness from waning protection is difficult.

Observational evidence of protection after vaccination among adolescents is also limited. Trial data for BNT162b2 in adolescents 12 to 15 years old showed 100% efficacy against documented infection. Emergency Use Authorization (EUA) was issued for this group on May 10, 2021.15

Assessments of the association between COVID-19 vaccination and SARS-CoV-2 infection that separately examine the effects of time since vaccination and of emerging variants can inform decisions regarding booster doses, variant-specific vaccine formulations, and other pandemic mitigation measures. This analysis used data from a national pharmacy-based COVID-19 testing platform to estimate product- and age group–specific associations between vaccination and symptomatic infection by time since vaccination before and during Delta variant predominance.

Methods
The human participants research advisor for the Centers for Disease Control and Prevention’s (CDC) National Center for Immunization and Respiratory Diseases determined this analysis met the requirements for public health surveillance as outlined in 45 CFR §46.102(l)(2). Because data were collected during routine operational procedures, this secondary data analysis did not require informed consent and was conducted consistent with applicable federal law and CDC policy.

Data Source
Data from the Increasing Community Access to Testing 2.0 platform—a Department of Health and Human Services (HHS) partnership facilitating no-cost, drive-through SARS-CoV-2 testing at pharmacies across all 50 states, the District of Columbia, and Puerto Rico—were analyzed. Testing sites were selected by HHS to prioritize access in racially and ethnically diverse communities and areas with moderate to high social vulnerability.

Individuals registered online for testing and self-reported demographic information; presence of COVID-19-like illness symptoms (eTable 1 in the Supplement); and since March 2021, vaccination status, including product received and number and dates of doses. From March to November 2021, data collection only allowed for self-reporting of 1 dose or 2 BNT162b2 or mRNA-1273 doses; booster doses were not reported. Vaccination reporting was not mandatory, and information was not verified.

Nasal swabs were tested for SARS-CoV-2 using rapid point-of-care tests or sent to laboratories for nucleic acid amplification testing (NAAT). Data were reported to HHS with an estimated 3-day lag and included test type, specimen collection date, test result, symptom status (asymptomatic, symptomatic [≥1 symptom], not reported), vaccination status, race and ethnicity (required data elements per HHS COVID-19 laboratory reporting requirements) from fixed categories provided by the pharmacy, sex, age group (prespecified as 12-15, 16-19, 20-44, 45-54, 55-64, ≥65 years), and county and state of residence. Data also included testing site zip code, county, state, and census tract social vulnerability index (SVI). No personally identifying information was reported.

Study Design
A retrospective test-negative, case-control analysis using laboratory-based NAATs collected through October 17, 2021, from persons reporting 1 or more COVID-19–like symptoms was conducted. The unit of analysis was tests; NAATs with positive results were classified as cases, and NAATs with negative results as controls. NAATs with indeterminate results were excluded.

The start date varied by age group: March 13, 2021, for tests for persons 20 years and older (based on vaccination data availability); April 15, 2021, for persons 16 to 19 years old (before that age 0-19 years were reported in aggregate); and June 15, 2021, for persons 12 to 15 years old (the earliest date this group could be fully vaccinated based on BNT162b2 EUA date). Tests came from 3 pharmacy chains (A, B, and C); 2 of the chains (A and B) contributed data throughout the entire analysis period while 1 (C) provided eligible tests beginning June 16, 2021.

Exposure
The exposure of interest was full vaccination with BNT162b2, mRNA-1273, or Ad26.COV2.S. Cases and controls were considered unvaccinated if tests were from persons reporting receipt of no COVID-19 vaccine, and fully vaccinated if tests were from persons reporting receipt of 1 dose of Ad26.COV2.S or 2 doses of mRNA vaccine, with reported date of receipt 14 days before and during Delta variant predominance.

Key Points
Question How does the association between prior COVID-19 vaccination and symptomatic SARS-CoV-2 infection change with time since vaccination and the SARS-CoV-2 Delta variant?

Findings In this test-negative, case-control study that included 1634 271 tests from symptomatic adults, the odds ratio for prior mRNA vaccination and SARS-CoV-2 test positivity was lower before than during Delta variant predominance. The attenuation in effect size related to time since vaccination was greater than the attenuation related to the Delta variant.

Meaning The findings are consistent with a steady decline in estimated mRNA vaccine effectiveness over time, separate from variant-specific differences in protection.

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or more before testing. Tests from persons reporting receipt of a COVID-19 vaccine but who were not fully vaccinated at time of testing, with missing vaccination status, or with illogical or missing vaccination details were excluded.

**Outcome**
The primary outcome measure was symptomatic SARS-CoV-2 infection determined by laboratory-based NAAT result. Time periods for the outcome were defined based on percentage of the Delta variant among US sequenced SARS-CoV-2 specimens: pre-Delta (<14%: March 13-May 29, 2021), intermediate (14%-90%: May 30-July 17, 2021), and Delta (>90%: July 18-October 17, 2021).

**Statistical Analysis**
Vaccine product-specific association between symptomatic infection and vaccination was estimated by comparing the odds of prior full vaccination (exposed) vs no vaccination (unexposed) in cases vs controls using multivariable logistic regression. The odds ratio (OR) was used to estimate vaccine effectiveness (VE), where VE = (1 – OR) × 100%. ORs by time since vaccination were modeled using a 2-knot quadratic spline for the number of days since full vaccination. ORs were estimated both stratified by age group and for all adults 20 years and older adjusted by age group. The 16- to 19-year age group did not align with mRNA-1273 or Ad26.COV2.S EUA specifications for use among those 18 years and older; therefore, vaccinated individuals were likely 18 to 19 years old, while unvaccinated individuals could have been 16 to 19 years old.21,22 Models were stratified by period (pre-Delta, intermediate, and Delta). Models included race, ethnicity, sex, testing site state, testing site census tract SVI, and test date as covariates to adjust for potential confounding. Unknown race and ethnicity were coded as categories of each variable and missing sex was included with other sex to retain these tests in models. Tests with other missing variables were included in unadjusted estimates but dropped from adjusted models.

To summarize changes in the association between symptomatic infection and full vaccination based on fitted curves, the following were calculated: (1) an initial OR reflecting the mean of the daily OR estimates from days 14 to 60 following the second dose) among adults 20 years and older during the Delta period to tests performed through September 23, before widespread access to boosters (eFigure 1 in the Supplement). To assess whether the addition of tests from pharmacy chain C starting June 16, 2021, affected pre-Delta/Delta comparisons, a sensitivity analysis was conducted for both periods excluding pharmacy chain C (eFigures 2-4 in the Supplement).

For comparability with other studies, discrete unadjusted and adjusted ORs for periods since final dose, starting at 14 to 30 days after the last dose and in subsequent 30-day increments, stratified by age group, product, and period were calculated (eTables 2-10 in the Supplement). For adolescent age groups in the pre-Delta and intermediate periods, data were too sparse to estimate ORs by day since vaccination, so only discrete estimates were calculated.

Statistical analyses were performed in R (version 4.0.2; R Foundation). The estimated ORs and their corresponding uncertainty are presented with point estimates and 95% CIs. Two-sided P values comparing the magnitude of the association between vaccination and infection across products and study periods for adults 20 years and older were corrected for multiple comparisons using Benjamini-Hochberg false discovery rate, and to account for the possibility of intraclass correlation due to repeat testing by the same individual a conservative P value threshold of less than .001 rather than less than .05 was considered significant.

**Results**
From March 13 to October 17, 2021, 1,814,383 tests from 6,884 sites nationwide met inclusion criteria (Figure 1), including 390,762 test-positive cases (21.5%) and 1,423,621 test-negative controls (78.5%) (59.9% aged 20-44 years, 9.9% aged 12-19 years; 58.9% female; 1.0% American Indian/Alaska Native, 6.5% Asian, 12.3% Black/African American, 0.7% Native Hawaiian or Other Pacific Islander, 71.8% White; 20.1% Hispanic/Latino). Records excluded for unknown vaccination status (8%) were similar to those with known status (eTables 11-12 in the Supplement). A total of 560,557 tests (30.9%) were from persons fully vaccinated with BNT162b2, 331,350 (18.3%) with mRNA-1273, and 75,583 (4.2%) with Ad26.COV2.S and 846,893 (46.7%) from unvaccinated persons. Cases were more frequently tests from persons who were male, Black/African American, from the South Atlantic region, and tested at sites with census tract SVI of 0.5 or greater indicating higher social vulnerability (Table).

**Adults 20 Years and Older**
Among adults 20 years and older, 499,879 (30.6%) were fully vaccinated with BNT162b2, 324,601 (19.9%) with mRNA-1273, and 73,709 (4.5%) with Ad26.COV2.S and 736,082 (45.0%) were unvaccinated. For BNT162b2 during the pre-Delta period, the initial OR between symptomatic infection and full vaccination (mean daily OR during days 14-60 since second dose) among adults 20 years and older was 0.10 (95% CI, 0.09-0.11) (eTable 13 in the Supplement), and the OR increased by a mean of 0.04 (95% CI, 0.02-0.05) per month...
during days 14 to 111, reflecting a weakening association over time since vaccination (Figure 2A). During the Delta period (July 18-October 17, 2021), the BNT162b2 initial OR was 0.16 (95% CI, 0.16-0.17), and the OR increased by 0.03 (95% CI, 0.02-0.03) per month from days 14 to 280. During the pre-Delta period, the mRNA-1273 initial OR was 0.05 (95% CI, 0.04-0.05), and the OR increased by 0.02 (95% CI, 0.005-0.03) per month from days 14 to 93 (Figure 2B). During the Delta period, the mRNA-1273 initial OR was 0.10 (95% CI, 0.10-0.11), and the OR increased by 0.03 (95% CI, 0.03-0.04) per month from days 14 to 266. For both mRNA vaccines, models for ages 20 to 44, 45 to 54, and 55 to 64 years yielded similar OR estimates and trends over time since the second dose within each period (Figure 3).

Among adults 65 years and older during the pre-Delta period, the initial OR between symptomatic infection and full vaccination for BNT162b2 was 0.11 (95% CI, 0.08-0.14) (eTable 13 in the Supplement) and the OR increased by 0.04 (95% CI, 0.01-0.08) per month from days 14 to 83 after the second dose (Figure 3D). During the Delta period, the initial BNT162b2 OR was 0.27 (95% CI, 0.22-0.31) and did not significantly increase (per-month change in OR, 0.00 [95% CI, -0.01 to 0.01] from days 14-260). For mRNA-1273, the initial OR was 0.05 (95% CI, 0.03-0.06) during the pre-Delta period and 0.21 (95% CI, 0.15-0.26) during the Delta period and did not significantly increase in either period (per-month change in OR, pre-Delta: -0.06 [95% CI, -0.14 to 0.02] from days 14-55; Delta: 0.00 [95% CI, -0.01 to 0.01] from days 14-254) (Figure 3H).

For Ad26.COV2.S, the initial OR between symptomatic infection and full vaccination during the pre-Delta period among adults 20 years and older was 0.42 (95% CI, 0.37-0.47) and the OR decreased nonlinearly from days 14 to 66 (Figure 2C; eTable 13 in the Supplement). During the Delta period, the initial OR was 0.62 (95% CI, 0.58-0.65) and the OR decreased nonlinearly from days 14 to 224 after vaccination.

Comparisons of vaccine products between periods for adults 20 years and older demonstrated that initial ORs were significantly lower during the pre-Delta vs Delta period for all products (P < .001; eTable 14 in the Supplement). Comparisons between products within the same time period demonstrated that initial ORs were significantly lower in both the pre-Delta and Delta periods for mRNA-1273 vs BNT162b2 (P < .001), for BNT162b2 vs Ad26.COV2.S (P < .001), and for mRNA-1273 vs Ad26.COV2.S (P < .001; eTable 14 in the Supplement).
Sensitivity analyses excluding pharmacy chain C and restricting the BNT162b2 model for adults 20 years and older during the Delta period to tests performed through September 23, 2021, yielded similar magnitudes of association and patterns over time (eFigures 1-4 in the Supplement). Estimates of ORs during the intermediate period for all products are shown in eFigures 5-6 in the Supplement.

**Adolescents 12 to 19 Years Old**

Among 180,112 adolescents 12 to 19 years old, 60,678 (33.7%) were fully vaccinated with BNT162b2, 6749 (3.7%) with mRNA-1273, and 1874 (1.0%) with Ad26.COV2.S and 110811 (61.5%) were unvaccinated (eTable 15 in the Supplement). During the

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**Table. Characteristics of Included Cases and Controls Tested for SARS-CoV-2 in Increasing Community Access to Testing (ICATT) 2.0, United States, March 13-October 17, 2021**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SARS-CoV-2, No. (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Positive cases</td>
<td>Negative controls</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>390 762</td>
<td>1 423 621</td>
<td></td>
</tr>
<tr>
<td>Age group, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-15a</td>
<td>14 988 (3.8)</td>
<td>56 216 (3.9)</td>
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<tr>
<td>16-19b</td>
<td>24 434 (6.3)</td>
<td>84 474 (5.9)</td>
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<tr>
<td>20-44</td>
<td>235 430 (60.2)</td>
<td>851 641 (59.8)</td>
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<tr>
<td>45-54</td>
<td>53 868 (13.8)</td>
<td>186 748 (13.1)</td>
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<tr>
<td>55-64</td>
<td>39 401 (10.1)</td>
<td>149 483 (10.5)</td>
<td></td>
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<tr>
<td>≥65</td>
<td>22 641 (5.8)</td>
<td>95 059 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>204 129 (52.3)</td>
<td>862 587 (60.7)</td>
<td></td>
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<tr>
<td>Male</td>
<td>186 044 (47.7)</td>
<td>556 959 (39.2)</td>
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<tr>
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<td>207 (0.1)</td>
<td>875 (0.1)</td>
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<td>Race</td>
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<td>13 247 (1.0)</td>
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<td>Asian</td>
<td>13 705 (3.8)</td>
<td>94 690 (7.2)</td>
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<tr>
<td>Black or African American</td>
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<td>153 806 (11.6)</td>
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<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>2798 (0.8)</td>
<td>9419 (0.7)</td>
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<tr>
<td>White</td>
<td>258 580 (72.0)</td>
<td>947 561 (71.7)</td>
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<tr>
<td>Other</td>
<td>26 149 (7.3)</td>
<td>102 279 (7.7)</td>
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</tr>
<tr>
<td>Ethnicity</td>
<td>356 181</td>
<td>1 301 519</td>
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<tr>
<td>Hispanic/Latino</td>
<td>74 971 (21.0)</td>
<td>257 432 (19.8)</td>
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<tr>
<td>Region</td>
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<tr>
<td>New England</td>
<td>10 706 (2.7)</td>
<td>73 588 (5.2)</td>
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<tr>
<td>Mid-Atlantic</td>
<td>58 293 (14.9)</td>
<td>251 553 (17.7)</td>
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<tr>
<td>South Atlantic</td>
<td>76 872 (19.7)</td>
<td>219 527 (15.4)</td>
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<tr>
<td>East North Central</td>
<td>65 966 (16.9)</td>
<td>227 916 (16.0)</td>
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<tr>
<td>East South Central</td>
<td>20 243 (5.2)</td>
<td>50 529 (3.5)</td>
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<tr>
<td>West North Central</td>
<td>16 424 (4.2)</td>
<td>73 745 (5.2)</td>
<td></td>
</tr>
<tr>
<td>West South Central</td>
<td>33 408 (8.5)</td>
<td>85 493 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Mountain</td>
<td>26 824 (6.9)</td>
<td>99 393 (7.0)</td>
<td></td>
</tr>
<tr>
<td>Pacific</td>
<td>81 569 (20.9)</td>
<td>33 878 (23.8)</td>
<td></td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>457 (0.1)</td>
<td>3403 (0.2)</td>
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</tr>
<tr>
<td>Site census tract SVI</td>
<td>390 110</td>
<td>1 419 346</td>
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</tr>
<tr>
<td>SVI &lt;0.5 (less socially vulnerable)</td>
<td>161 022 (41.3)</td>
<td>649 521 (45.8)</td>
<td></td>
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<tr>
<td>SVI, 0.5-1.0 (more socially vulnerable)</td>
<td>229 088 (58.7)</td>
<td>769 825 (54.2)</td>
<td></td>
</tr>
<tr>
<td>Vaccination status</td>
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</tr>
<tr>
<td>Unvaccinated</td>
<td>276 336 (70.7)</td>
<td>570 557 (40.1)</td>
<td></td>
</tr>
<tr>
<td>Ad26.COV2.S fully vaccinated</td>
<td>15 587 (4.0)</td>
<td>59 996 (4.2)</td>
<td></td>
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<tr>
<td>mRNA fully vaccinated</td>
<td>98 839 (25.3)</td>
<td>793 068 (55.7)</td>
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</tr>
<tr>
<td>BNT162b2 fully vaccinated</td>
<td>68 214 (17.5)</td>
<td>492 343 (34.6)</td>
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<tr>
<td>mRNA-1273 fully vaccinated</td>
<td>30 625 (7.8)</td>
<td>300 725 (21.1)</td>
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(continued)
Delta period among adolescents 12 to 15 years old, the BNT162b2 initial OR between symptomatic infection and full vaccination was 0.06 (95% CI, 0.05-0.06), and the OR increased by 0.02 (95% CI, 0.01-0.03) per month from days 14 to 127 (Figure 4; eTable 13 in the Supplement). During the Delta period among adolescents 16 to 19 years old, the BNT162b2 initial OR was 0.10 (95% CI, 0.09-0.11), and the OR increased by 0.04 (95% CI, 0.03-0.06) per month from days 14 to 231. The mRNA-1273 initial OR among adolescents 16 to 19 years old was 0.06 (95% CI, 0.04-0.08), and the OR increased by 0.03 (95% CI, 0.02-0.05) per month from days 14 to 203. The initial Ad26.COV2.S OR among adolescents 16 to 19 years old was 0.46 (95% CI, 0.30-0.62) and was stable over time since vaccination.

Discussion

In this analysis of SARS-CoV-2 tests performed at sites across the US from March 13 to October 17, 2021, among adults the OR for the association between symptomatic SARS-CoV-2 infection and vaccination (as an estimate of vaccine effectiveness) was higher during Delta variant predominance, suggesting lower protection. For mRNA vaccination, the steady increase in OR by month since vaccination was consistent with attenuation of effectiveness over time. The magnitude of the association between mRNA vaccination and symptomatic SARS-CoV-2 infection was less affected by the emergence of the Delta variant than by time since second dose of vaccine. Among adults, the ORs for mRNA vaccination increased by 0.02 to 0.04 per month, corresponding to a reduction in vaccine effectiveness of approximately 30% over 8 to 9 months. In adolescents 12 to 19 years old, the association between infection and mRNA vaccination similarly attenuated with time since vaccination. Booster doses are now recommended in the US for persons 12 years and older and may help optimize protection.

Other observational studies have reported declining protection from mRNA vaccines against infection and declining protection in the Delta period compared with the pre-Delta period but few could assess these effects separately because Delta emerged several months after initial vaccine introduction. In this analysis, the pattern of attenuation related to the time since vaccination for mRNA vaccines was consistent before and after the emergence of Delta as the predominant variant, although the initial ORs were higher during the Delta than pre-Delta periods. More recent data from this same testing platform suggest that 2 doses of mRNA vaccine offer less protection against infection with the Omicron variant than against infection with the Delta variant, but the pattern of attenuation over time since vaccination was similar for both variants. Together these data suggest that while the starting point for protection among recent recipients of 2 doses of mRNA
Figure 3. Association of COVID-19 Vaccination and Symptomatic SARS-CoV-2 Infection by Day Since Vaccination by Adult Age Group and Vaccine Product in the Pre-Delta and Delta Periods

Panels display odds ratios (ORs), plotted on a logarithmic scale, for prior COVID-19 vaccination (by age group and vaccine product) and SARS-CoV-2 test positivity by day since vaccination (starting at day 14 since second mRNA dose or Ad26.COV2.S dose) in the pre-Delta (March 13-May 29, 2021; shown in blue) and Delta (July 18-October 17, 2021; shown in orange) periods with 95% CIs (shaded areas). ORs were adjusted for race, ethnicity, sex, testing site, testing site census tract social vulnerability index, and calendar date as a continuous variable. Tests with missing social vulnerability index were excluded from adjusted analyses. The presented (fitted) curves were truncated on the day after which 10 or fewer cases remained for each product-, age group–, and period-specific model, beyond which CIs widened. For Ad26.COV2.S, the y-axis was truncated at 2.0, and data points above 2.0 are not shown. ORs (95% CIs) for day 14, mean of the daily OR estimates from days 14 to 60 (initial OR), and end day for each period are shown in eTable 13 in the Supplement.
vaccine can differ across variants, declines in effectiveness over time may be more predictable. It will be important to evaluate whether protection from booster doses wanes in a similar fashion as that of 2 doses.

In this analysis, the magnitude of the association between vaccination and infection was greater for mRNA-1273 than for BNT162b2. Early observational data found nearly identical estimates for the association between mRNA-1273 and BNT162b2 vaccination and infection, but evidence during the Delta period suggests that mRNA-1273 vaccination may be more protective against both infection and hospitalization than BNT162b2 vaccination. Important differences between these vaccines include the mRNA dose (mRNA-1273, 100 μg; BNT162b2, 30 μg) and dosing interval (mRNA-1273, 28 days; BNT162b2, 21 days). Further investigation of the reasons for differing protection is needed to guide product-specific recommendations.

For Ad26.COV2.S, the initial OR was higher than that of both mRNA vaccines, consistent with lower vaccine effectiveness, but there was no attenuation over time. Additionally, the initial OR was higher during the Delta than pre-Delta period, suggesting reduced protection against the Delta variant. Although in this analysis fewer tests were from persons who received Ad26.COV2.S compared with the mRNA vaccines, these results add to the limited number of observational Ad26.COV2.S studies. These studies have reported effectiveness for Ad26.COV2.S against infection (with or without symptoms) ranging from 50% to 87%, and stable protection over time. Booster doses are now recommended for all Ad26.COV2.S recipients 2 months or more after vaccination. Additional evaluations are needed to estimate effectiveness of a 2-dose Ad26.COV2.S schedule as well as protection against newly emerging variants such as Omicron.

This analysis also adds to limited observational evidence on COVID-19 vaccines in adolescents. In this analysis, the ORs since the second mRNA dose remained 0.11 or less for adolescents 12 to 15 years old over a period of 4 months and 0.38 or less for adolescents 16 to 19 years old over a period of 7.5 months, corresponding to an estimated mRNA vaccine effectiveness of 89% or more and 62% or more, respectively. This supports continued efforts to increase vaccine coverage of both the primary series and booster doses in adolescents.

Among adults 65 years and older, the association between mRNA vaccination and symptomatic infection was stable over time since vaccination during the Delta period. This finding contrasts with other studies reporting waning protection from BNT162b2 among older adults. During the Delta period, the observed BNT162b2 OR decreased for older adults at about 6 months after the second dose, which might be attributable to booster doses (not captured in these data) recommended on September 23, 2021, for older adults more than 6 months after their primary series. However, the sensitivity analysis that only included tests from before the authorization of booster doses yielded similar results. The results for adults 65 years and older should be interpreted with caution due to low numbers of recently vaccinated older adults at about 6 months after the second dose, which might be attributable to booster doses (not captured in these data) recommended on September 23, 2021, for older adults more than 6 months after their primary series. However, the sensitivity analysis that only included tests from before the authorization of booster doses yielded similar results. The results for adults 65 years and older should be interpreted with caution due to low numbers of recently vaccinated older
adults during Delta predominance and because older adults tested at drive-through sites may differ from the general older adult population.

Limitations
This study had additional limitations. First, vaccination status and symptoms were based on self-report, potentially leading to misclassification. Second, exclusion of tests from persons with missing vaccination status (8%) could introduce bias due to differences in behavior and COVID-19 risk. Third, this analysis could not account for some potentially important confounders including underlying conditions, prior COVID-19 disease, and mitigation behaviors such as masking, which likely changed with changing public health guidance for vaccinated individuals.23,24 Fourth, the likelihood of testing might change over time or with vaccination status; however, as long as it did not differ systematically between individuals with COVID-19 and non–COVID-19 acute respiratory infections, these changes would not cause bias.25 Fifth, because these data do not include identifiers, test was used as the unit of analysis and individuals may have been included more than once. However, a more restrictive significance threshold of P less than .001 was used to account for the possibility of intra-individual correlation in significance tests.

Sixth, within the 16- to 19-year age group, those vaccinated with mRNA-1273 or Ad26.COV2.S were likely 18 to 19 years old, while unvaccinated persons may have been 16 to 19 years old, due to differences between prespecified age groups in this data set and EUA age cutoffs.21,22 Seventh, vaccination eligibility varied by jurisdiction; some tests in March and April 2021 may have been from those not yet eligible for vaccination. Eighth, these data do not include sequencing results, so time was used as a proxy for Delta infection, similar to other analyses.27,28,34 Ninth, the inclusion of pharmacy chain C’s tests starting June 16, 2021 (57% of tests), may have affected the comparability of pre-Delta and Delta results. However, the sensitivity analysis conducted excluding pharmacy chain C showed similar results. Tenth, during the time of this study, the Increasing Community Access to Testing platform did not allow for reporting of more than 2 vaccine doses; some individuals may have received additional or booster doses that were not recorded.

Conclusions
Among adults, the OR for the association between symptomatic SARS-CoV-2 infection and COVID-19 vaccination (as an estimate of vaccine effectiveness) was higher during Delta variant predominance, suggesting lower protection. For mRNA vaccination, the steady increase in OR by month since vaccination was consistent with attenuation of estimated effectiveness over time; attenuation related to time was greater than that related to variant.

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Original Investigation Research


