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RESEARCH ARTICLE

Association Between mRNA Vaccination and Infection From SARS-CoV-2 During the Delta and Omicron BA.1 Waves: A Population-Level Analysis

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Introduction: COVID-19 mRNA vaccine protection against the Omicron variant of SARS-CoV-2 has been shown to be attenuated. Previous research in Shelby County, Tennessee found that vaccine effectiveness might differ by age in the Omicron surge, a finding not reported for other variants. To assess whether patterns in vaccine effectiveness by age group differed on the basis of the predominant strain of SARS-CoV2, we evaluated vaccine effectiveness in Shelby County, Tennessee by age group in the Delta wave and Omicron BA.1 (Omicron) wave.

Methods: Case and vaccination statuses of residents were assessed using COVID-19 surveillance data. Age was stratified as 18–34, 35–64, and ≥65 years. Vaccination groups included unvaccinated, fully vaccinated, and fully vaccinated + booster. Person time was counted in each wave by vaccination status until the time of a positive reported COVID-19 test or until the end of the study period.

Results: Incidence of COVID-19 was much higher during the Omicron wave than during the Delta wave across all vaccination groups. During the Delta wave, among adults, 79.2% fewer cases were identified in those fully vaccinated and 94.8% fewer in those fully vaccinated + booster, compared with 40.2% and 66.7%, respectively, in the Omicron wave, compared with those who were unvaccinated.

Conclusions: This study found evidence that vaccine effectiveness differed by age group during the Omicron wave, where the same pattern was not prominent in the Delta wave. Further analysis investigating the influence of behavior patterns and other potential confounders on vaccine effectiveness would be useful in further understanding the relationship between age and vaccine effectiveness.

INTRODUCTION

Two mRNA-based coronavirus disease 2019 (COVID-19) vaccines significantly reduced symptomatic COVID-19 cases from the original strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in clinical trials and have been approved by the U.S. Food and Drug Administration for use in adults since mid-December 2020.[1,2] With the Omicron variant of SARS-CoV-2

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as the dominant strain worldwide in 2022, evidence from clinical and epidemiologic studies suggest that vaccine protection is attenuated compared with the protection against previously circulating variants.[3–7] Previous research in Shelby County, Tennessee found that vaccine effectiveness (VE) might differ by age in the context of the Omicron surge, a finding which had not been reported in previous waves.[7] To assess whether patterns in VE by age group differed on the basis of the predominant strain of SARS-CoV-2, we evaluated VE by age group in the period when the Delta variant was predominant compared with that in the period when the Omicron BA.1 variant was predominant.

METHODS

Study Population

We applied the same methodology previously described in our pilot study of VE among adults (those aged ≥18 years) by age group[7] during the first 6 weeks of the Omicron surge to the entire timeframe of the Omicron BA.1 wave (from December 12, 2021 through March 31, 2022) and to the entire timeframe of the Delta wave (from July 1, 2021 through November 30, 2021) in Shelby County, Tennessee. Case and vaccination statuses of Shelby County residents were assessed using COVID-19 surveillance data as described in our previous work.[7]

Measures

Age was stratified as 18–34, 35–64, and ≥65 years. Vaccination status groups evaluated were those who were unvaccinated, including individuals who received no vaccination for COVID-19; those who were fully vaccinated, including individuals who had completed the primary mRNA vaccination series and were considered fully vaccinated 14 days after administration of their second dose but had not received an additional mRNA vaccine dose; and those who received full vaccination + booster, including individuals who were fully vaccinated with an mRNA vaccine option and had also received at least 1 additional dose of mRNA vaccine. Confirmed or probable case status was ascertained from daily surveillance case files, including all reported clinically administered positive test results (i.e., polymerase chain reaction and antigen tests).

Statistical Analysis

For the Delta and Omicron BA.1 timeframes, person time was counted by vaccination status until the time that the individual tested positive for COVID-19, at which point they contributed a case, or the study period ended, at which point they were censored. Individuals could contribute person time to more than 1 vaccination status exposure group. In this case, when the person's vaccination status changed and they had not previously become a case during the study follow-up time, they no longer contributed person time to the initial vaccination status and began contributing time to the new vaccination status group until the point that they became a case, the study period ended, or they further changed vaccination status. Those who received a non-mRNA vaccine option or who had documented vaccination with an unknown type were excluded from the analysis.

Statistical methods included incidence rates (IRs) and IR ratios (IRRs) on the basis of the numbers of cases and person years at risk within each stratum. VE was calculated as 1 − IRR. Estimates include 95% CIs (alpha level of 0.05). Analyses were conducted in R, Version 4.2 (R Core Team).

RESULTS

Shelby County has a diverse population of nearly 1 million residents.[8] The demographic makeup of the county is roughly 60% Black or African American, 40% White, and 7% Hispanic/Latino.[8] Approximately 25% of the population is aged <18 years, and about 15% is aged ≥65 years.[8] We excluded 19,171 individuals from the analysis owing to unknown vaccine type or vaccination with a non-mRNA vaccine option, representing <3% of the total adult population.

During the Delta wave, 320,940 adults contributed 101,509 person years of follow-up time to the unvaccinated group; 391,177 adults contributed 131,754 person years of follow-up time to the fully vaccinated group; and 93,397 adults contributed 9,565 person years of follow-up time to the fully vaccinated + booster group. During the Omicron BA.1 wave, 207,765 adults contributed 51,862 person years of follow-up time to the unvaccinated group; 300,661 adults contributed 67,829 person years of follow-up time to the fully vaccinated group; and 185,929 adults contributed 48,652 years of follow-up time to the fully vaccinated + booster group. Individuals were able to contribute time to multiple vaccination status groups in both waves.

The IR of COVID-19 per 100 person years of follow-up time (95% CI) was much higher during the Omicron BA.1 wave than during the Delta wave, across all vaccination status groups. In the unvaccinated group, the IR was 54 (95% CI=53, 55) during the Omicron BA.1 wave, compared with 24 (95% CI=23, 24) during the Delta wave for all adults (aged ≥18 years). In the fully vaccinated group, the IR among all adults was 32 (95% CI=32, 33) during the Omicron BA.1 wave compared with 5 (95% CI=5, 5) during the Delta wave. Furthermore, in the fully vaccinated + booster group, the IR

Table 1. Incidence Rate per 100 Years of Person Time by Vaccination Status, Age Group, and Wave

Age group, years	Incidence rate (95% CI) unvaccinated	Incidence rate (95% CI) fully vaccinated	Incidence rate (95% CI) fully vaccinated + booster	Incidence rate (95% CI) unvaccinated	Incidence rate (95% CI) fully vaccinated	Incidence rate (95% CI) fully vaccinated + booster
		Delta			Omicron	
18–34	23 (22, 23)	5 (5, 5)	2 (1, 3)	47 (46, 48)	37 (36, 38)	24 (23, 26)
35–64	25 (25, 26)	5 (5, 5)	1 (1, 2)	61 (60, 62)	34 (33, 34)	21 (21, 22)
≥65	19 (18, 19)	5 (4, 5)	1 (1, 1)	69 (66, 71)	19 (18, 20)	12 (11, 12)
Overall ≥18	24 (23, 24)	5 (5, 5)	1 (1, 2)	54 (53, 55)	32 (32, 33)	18 (18, 18)

among all adults was 18 (95% CI=18, 18) in the Omicron BA.1 wave compared with 1 (95% CI=1, 2) in the Delta wave. IRs by wave, vaccination status, and age group are shown in Table 1.

IRRs (95% CI) showed substantial protection against infection afforded by vaccination for both the fully vaccinated group and the fully vaccinated + booster group, with the most protection in both waves seen by those who received an additional dose. Adults in the fully vaccinated + booster group had an IRR of 0.333 (95% CI=0.325, 0.341) during the Omicron BA.1 wave, equating to a VE estimate (95% CI) of 66.7% (95% CI=65.9%, 67.5%) compared with that among those who were unvaccinated. Adults in the fully vaccinated group had an IRR of 0.598 (95% CI=0.587, 0.608) during the Omicron BA.1 wave, equating to a VE of 40.2% (95% CI=39.2%, 41.3%) compared with that among those who were unvaccinated. VE was much higher during the Delta wave than during the Omicron BA.1 wave for both vaccinated groups. During the Delta wave, adults in the fully vaccinated + booster group had an IRR of 0.052 (95% CI=0.043, 0.062), equating to a VE of 94.8% (95% CI=93.8, 95.7), and adults in the fully vaccinated group had an IRR of 0.208 (95% CI=0.202, 0.213), equating to a VE of 79.2% (95% CI=78.7, 79.8).

Age effects on protection afforded by vaccination are much more prominent in the Omicron BA.1 wave than in the Delta wave. During the Omicron BA.1 wave, VE in the fully vaccinated + booster group ranged from 47.8% (95% CI=44.9, 50.5) among those aged 18–34 years to 83.1% (95% CI=82.1, 84.1) among those age ≥65 years. During the Delta wave, VE in the fully vaccinated + booster group ranged from 92.3% (95% CI=87.1, 96.1) among those aged 18–34 years to 94.8% (95% CI=93.1, 96.1) among those aged 35–64 years. During the Omicron BA.1 wave, VE in the fully vaccinated group ranged from 21.3% (95% CI=19.0, 23.5) among those aged 18–34 years to 72.5% (95% CI=70.8, 74.0) among those age ≥65 years. During the Delta wave, VE in the fully vaccinated group ranged from 75.6% (95% CI=73.8, 77.2) among those aged ≥65 years to 80.2% (95% CI=79.4, 80.9) among those aged 35–64 years. Table 2 shows IRRs comparing both vaccinated exposure groups with the unvaccinated group by age group during both waves. Figure 1 and Table 3 show the VE point estimates by age group between the Delta and Omicron BA.1 waves.

DISCUSSION

The incidence of infection was dramatically different between waves, across all vaccination statuses. This analysis found that among unvaccinated adults, the incidence of infection during the Delta wave was less than

Table 2. Incidence Rate Ratio by Vaccination Status, Age Group, and Wave

Age group, years	Incidence rate ratio (95% CI) fully vaccinated versus unvaccinated	Incidence rate ratio (95% CI) fully vaccinated + booster versus unvaccinated	Incidence rate ratio (95% CI) fully vaccinated versus unvaccinated	Incidence rate ratio (95% CI) fully vaccinated + booster versus unvaccinated
	Delta		Omicron	
18–34	0.213 (0.202, 0.225)	0.077 (0.039, 0.129)	0.787 (0.765, 0.81)	0.522 (0.495, 0.551)
35–64	0.199 (0.191, 0.206)	0.052 (0.039, 0.069)	0.557 (0.543, 0.571)	0.351 (0.340, 0.363)
≥65	0.244 (0.228, 0.262)	0.057 (0.043, 0.074)	0.275 (0.26, 0.292)	0.169 (0.159, 0.179)
Overall ≥18	0.208 (0.202, 0.213)	0.052 (0.043, 0.062)	0.598 (0.587, 0.608)	0.333 (0.325, 0.341)

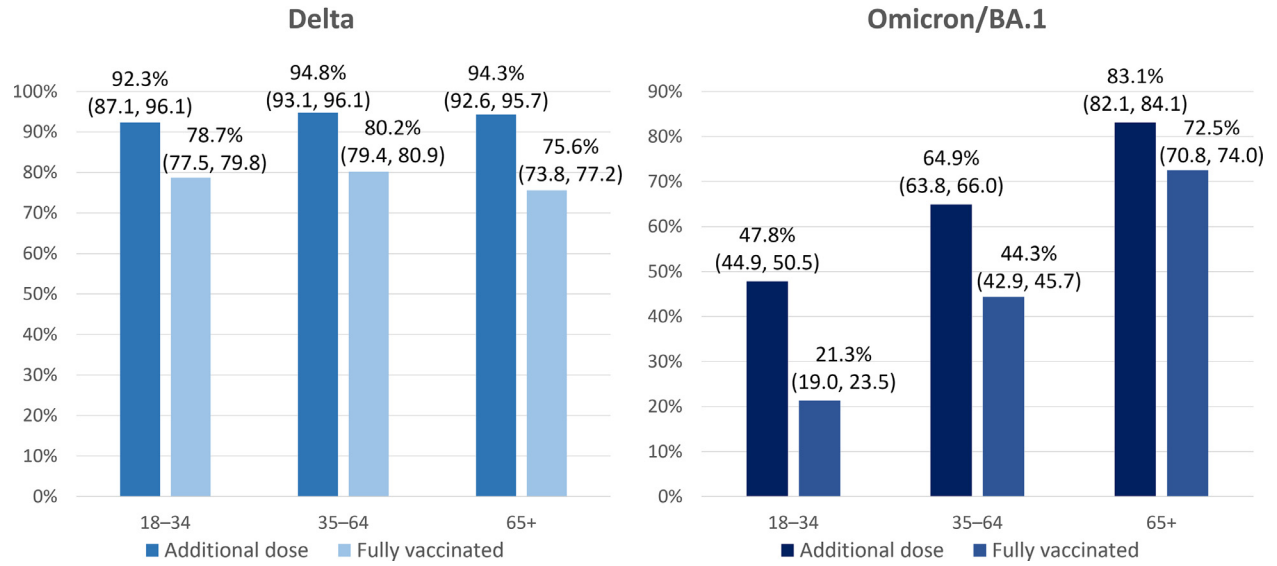

Figure 1. Vaccine effectiveness estimate (95% CI) by age group in the Delta and Omicron/BA.1 waves.

half (44.4%) of that during the Omicron BA.1 wave. Incidence of infection in adults was also substantially higher in the Omicron BA.1 wave than in the Delta wave among the fully vaccinated group and the fully vaccinated + booster group. The fully vaccinated group had 15.6% of the incidence of infection in the Delta wave that they had in the Omicron BA.1 wave, and among the fully vaccinated + booster group, the incidence of infection in the Delta wave was 5.6% of the incidence of infection during the Omicron wave. This suggests that the levels of protection conferred from vaccination differed between the Delta and the Omicron BA.1 waves in Shelby County. In addition, we found evidence that in the context of Omicron BA.1, vaccine protection differed by age group, where the same pattern is not prominent in the Delta wave.

Additional doses of COVID-19 vaccine were not authorized for use in the public for the entirety of the Delta wave, but by the end of the Delta wave study period (November 30, 2021), 90,353 people had received an additional dose. By the end of the Omicron BA.1 wave study period (March 31, 2022), 197,456 people had received an additional dose. This shows that nearly half (45.7%) of all people who would have received an additional dose by the end of the Omicron BA.1 wave had already done so by the end of the Delta wave.

At the beginning of the Delta wave, vaccine uptake in the population was quite varied by age group. Among those aged ≥65 years, at least 75% had received 1 dose or more of COVID-19 vaccine by July 1, 2021. Among those aged 35−64 years, that number ranged from 47.5% in those aged 35−44 years to 56.5% in those aged 45−54 years. Among adults aged <35 years, uptake ranged from 30% to 35% at that time. These differences by age group solidified and widened by the onset of the Omicron BA.1 surge. By December 12, 2021, >82% of

Table 3. Vaccine Effectiveness (%) by Vaccination Status, Age Group, and Wave

Age group, years	Vaccine effectiveness percentage estimate (95% CI) fully vaccinated versus unvaccinated	Vaccine effectiveness percentage estimate (95% CI) fully vaccinated + booster versus unvaccinated	Vaccine effectiveness percentage estimate (95% CI) fully vaccinated versus unvaccinated	Vaccine effectiveness percentage estimate (95% CI) fully vaccinated + booster versus unvaccinated
	Delta		Omicron	
18−34	78.66 (77.45, 79.81)	92.26 (87.06, 96.12)	21.28 (19, 23.49)	47.78 (44.93, 50.53)
35−64	80.15 (79.39, 80.89)	94.75 (93.14, 96.09)	44.29 (42.9, 45.66)	64.90 (63.75, 66.02)
≥65	75.56 (73.8, 77.21)	94.30 (92.60, 95.72)	72.46 (70.79, 74.03)	83.10 (82.09, 84.06)
Overall ≥18	79.24 (78.66, 79.81)	94.80 (93.83, 95.70)	40.22 (39.15, 41.28)	66.69 (65.89, 67.49)

Note: Vaccine effectiveness estimates are calculated as (1−incidence rate ratio) × 100.

those aged ≥65 years had received at least 1 dose of a COVID-19 vaccine. Among those aged 35−64 years, that number ranged from 67.3% to 77.6%, and in those aged 18−34 years, only about 50% have any vaccine uptake. This difference in vaccine uptake by age group could have significant impacts on exposure patterns of people within each of these age groups. If individuals within the cohort primarily socialize with other members of their age group, higher vaccine uptake in one age group could lower the overall risk of infection in that age group, thereby also lowering the risk of exposure within that age group. This could confound the association between vaccination and infection with COVID-19. Furthermore, this association could be confounded by differences in behavior and testing patterns between the 2 waves. Differences in behavior patterns could have been driven both by differences in public policy and by differences in perceived severity between the 2 waves because rates of hospitalizations, which were publicly reported, were substantially higher during the Delta wave than during the Omicron BA.1 wave. On October 27, 2021, county-wide mask requirements were lifted for public indoor settings in Shelby County. This was toward the end of the Delta wave, and further requirements were not reinstated in the context of the Omicron BA.1 wave. Our analysis is not able to assess VE by immune status (i.e., immunocompromised versus individuals with normal immune response) because this level of detail is not consistently available in our COVID-19 surveillance data. For the purposes of this analysis, immunocompromised people are included in the fully vaccinated + booster group at the point of their additional dose. This factor could cause underestimation of vaccine VEs in our analysis because those who are immunocompromised are recommended to receive an additional dose beyond the standard 2-dose primary series and before the booster dose.[9] In addition, access to home testing was more prominent through the Omicron timeframe than during the Delta wave, especially into the later months of the Omicron BA.1 wave, owing to public access to federally funded home test kits beginning in late January 2022 and greater general commercial availability of home test kits thereafter. Beyond the basic issue of availability of home tests, individual ability to correctly use at-home test kits is another factor that might influence clinical testing patterns between the 2 waves. Different versions of home test kits have varying levels of complexity and numbers of steps. Incorrect home test administration is likely to lead to false negative results, which may disincentivize individuals from seeking clinical testing, especially those experiencing mild symptoms. For example, a person who experienced mild symptoms in the context of the Delta wave may have been more likely to seek a clinically administered test than a person experiencing a similar level of symptoms during the Omicron wave, when home tests were widely available, especially if they had a false negative result from an incorrectly administered home test. These factors could have driven differences in behavior and testing patterns that could have further confounded the relationship between vaccination status and COVID-19 infection and led to differences in VE estimates between the Delta and Omicron BA.1 waves.

This study is not designed to specifically assess the impact of waning immunity from COVID-19 vaccination because we do not measure time from vaccination in the fully vaccinated and fully vaccinated + booster groups as part of our analysis. However, findings from a recently published systematic review and meta-analysis suggest that VE against both laboratory-confirmed and symptomatic COVID-19 infection is not only initially lower but also wanes more quickly in the context of the Omicron variant than in the Delta variant, with estimates of VE against laboratory-confirmed infection after primary series completion ranging from 44.4% (95% CI=37.7% −51.1%) after 1 month to 13.4% (95% CI=7.8%−18.9%) after 9 months with the Omicron variant and 80.5% (95% CI=75.3%−85.7%) after 1 month to 45.9% (95% CI=37.5%−54.2%) after 9 months with the Delta variant.[10] With respect to laboratory-confirmed infection, estimates of VE against the Omicron variant after administration of the booster dose were substantially higher and waned more slowly than after administration of the primary series, with estimates ranging from 55.4% (95% CI=42.4%−68.4%) 1 month after the booster to 28.9% (95% CI=17.1%−40.6%) 9 months after the booster.[10] These results are consistent with our findings.

Limitations

Our study has several limitations. Our calculations rely on the use of surveillance data for both vaccination and confirmed or probable case status, which is susceptible to under-reporting. In addition, census population estimates are used to inform the number of people in the population who have not had a reported case or reported COVID-19 vaccination history, as described in previous work.[7] This analysis is further limited by the fact that booster doses were not widely available to the general public for most of the Delta wave. Therefore, the generalizability of the findings related to VE in the fully vaccinated + booster group during the Delta wave is limited and is best interpreted as the observed population-level protection provided by booster doses in the limited time they were available during the Delta wave in Shelby County, Tennessee. The estimates produced by this analysis are crude and are not able to be adjusted for

important confounders and effect modifiers such as uptake and relative effectiveness of infection mitigation measures in place at the time, availability of additional vaccine doses, availability of home tests, race, and other demographic factors. However, our results are stratified by age group and illustrate the overall effectiveness of mRNA vaccination in our population in both the Delta and Omicron BA.1 waves of COVID-19.

CONCLUSIONS

Our analysis found that those with at least 1 additional dose of mRNA vaccine had the most protection against infection with SARS-CoV-2 in both the Delta and Omicron BA.1 waves. These findings further validate and support the utility of mRNA vaccination and booster doses in preventing SARS-CoV-2 infection. Results show that VE varied substantially by age group during the Omicron BA.1 wave, where the same pattern is not seen as clearly during the Delta wave. Further analysis investigating the influence of herd vaccine uptake and differing behavior pattern as well as other potential confounding factors such as demographic and socioeconomic factors on VE would be useful in further understanding the relationship between age and VE.

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CREDIT AUTHOR STATEMENT

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