ORIGINAL ARTICLE

Effectiveness of Covid-19 Vaccines over a 9-Month Period in North Carolina

Dan-Yu Lin, Ph.D., Yu Gu, B.S., Bradford Wheeler, M.P.H., Hayley Young, M.P.H., Shannon Holloway, Ph.D., Shadia-Khan Sunny, M.D., Ph.D., M.P.H., Zack Moore, M.D., M.P.H., and Donglin Zeng, Ph.D.

ABSTRACT

BACKGROUND

The duration of protection afforded by coronavirus disease 2019 (Covid-19) vaccines in the United States is unclear. Whether the increase in postvaccination infections during the summer of 2021 was caused by declining immunity over time, the emergence of the B.1.617.2 (delta) variant, or both is unknown.

METHODS

We extracted data regarding Covid-19–related vaccination and outcomes during a 9-month period (December 11, 2020, to September 8, 2021) for approximately 10.6 million North Carolina residents by linking data from the North Carolina Covid-19 Surveillance System and the Covid-19 Vaccine Management System. We used a Cox regression model to estimate the effectiveness of the BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna), and Ad26.COV2.S (Johnson & Johnson–Janssen) vaccines in reducing the current risks of Covid-19, hospitalization, and death, as a function of time elapsed since vaccination.

RESULTS

For the two-dose regimens of messenger RNA (mRNA) vaccines BNT162b2 (30 μg per dose) and mRNA-1273 (100 μg per dose), vaccine effectiveness against Covid-19 was 94.5% (95% confidence interval [CI], 94.1 to 94.9) and 95.9% (95% CI, 95.5 to 96.2), respectively, at 2 months after the first dose and decreased to 66.6% (95% CI, 65.2 to 67.8) and 80.3% (95% CI, 79.3 to 81.2), respectively, at 7 months. Among early recipients of BNT162b2 and mRNA-1273, effectiveness decreased by approximately 15 and 10 percentage points, respectively, from mid-June to mid-July, when the delta variant became dominant. For the one-dose regimen of Ad26.COV2.S (5×10^{10} viral particles), effectiveness against Covid-19 was 74.8% (95% CI, 72.5 to 76.9) at 1 month and decreased to 59.4% (95% CI, 57.2 to 61.5) at 5 months. All three vaccines maintained better effectiveness in preventing hospitalization and death than in preventing infection over time, although the two mRNA vaccines provided higher levels of protection than Ad26.COV2.S.

CONCLUSIONS

All three Covid-19 vaccines had durable effectiveness in reducing the risks of hospitalization and death. Waning protection against infection over time was due to both declining immunity and the emergence of the delta variant. (Funded by a Dennis Gillings Distinguished Professorship and the National Institutes of Health.)

From the Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill (D.-Y.L., Y.G., D.Z.), and the North Carolina Department of Health and Human Services (B.W., H.Y., Z.M.), North Carolina State University (S.H.), and the CDC Foundation, North Carolina Department of Health and Human Services (S.-K.S.), Raleigh. Dr. Lin can be contacted at lin@bios.unc.edu or at the Department of Biostatistics, University of North Carolina at Chapel Hill, 3101E McGavran-Greenberg Hall, Chapel Hill, NC 27599.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in more than 50 million cases of coronavirus disease 2019 (Covid-19) and more than 800,000 deaths in the United States alone. One key step to ending this pandemic is the deployment of durably effective vaccines. Between December 2020 and February 2021, three Covid-19 vaccines — BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna), and Ad26.COV2.S (Johnson & Johnson–Janssen) — received Emergency Use Authorization from the Food and Drug Administration on the basis of short-term safety and efficacy against Covid-19,[1-3] and the vaccines were deployed in the United States soon thereafter. However, an increase in postvaccination SARS-CoV-2 infections during the summer and early fall of 2021 aroused concerns about the long-term effectiveness of these vaccines, as well as their effectiveness against new variants, such as the B.1.617.2 (delta) variant.

Several observational studies have assessed the waning effectiveness of Covid-19 vaccines over time.[4-12] These studies typically included estimates of vaccine effectiveness for broad time periods (1 to 3 months), and the confidence intervals for different time periods usually overlapped, such that the levels of waning were unclear. In addition, most of these studies were not large enough to determine whether the waning effectiveness was due to declining immunity from the primary vaccine series, the emergence of new and more transmissible variants, or both.

Surveillance systems in the United States are designed to capture the Covid-19–related vaccination history and clinical outcomes for all residents, and these systems provide valuable resources for assessing the effectiveness of Covid-19 vaccines in a real-world setting. On the basis of surveillance data from the entire state of North Carolina, which has a population of approximately 10.6 million people, we estimated the effectiveness of the three Covid-19 vaccines currently deployed in the United States in reducing the risks of Covid-19, hospitalization, and death up to 9 months after vaccination.

Methods

Data Sources

The state of North Carolina collects data from several sources and partners to monitor the Covid-19 pandemic in the state. The following data sources were used in our study.

North Carolina Covid-19 Surveillance System

The North Carolina Covid-19 Surveillance System (NC COVID) is a Web-based central repository of person-level laboratory and communicable-disease investigation data used by the Division of Public Health at the North Carolina Department of Health and Human Services and by the 86 local and multicounty district health departments in the state. Laboratories report Covid-19 test results to NC COVID electronically; when the results of polymerase-chain-reaction or antigen testing meet the case definition, investigation workflows are initiated. Local health departments attempt to gather additional demographic and clinical outcomes data. Data from NC COVID are shared with the Centers for Disease Control and Prevention through the National Notifiable Disease Surveillance System.

Covid-19 Vaccine Management System

Information regarding persons who have been vaccinated in North Carolina is collected in the Covid-19 Vaccine Management System (CVMS), a secure, cloud-based system that enables vaccine management and data sharing across recipients, care providers, hospitals, agencies, and local, state, and federal governments on one common platform. The system tracks information about provider enrollment and vaccine products administered, schedules appointments according to the recommended vaccination schedule, and allows the state to manage vaccine supply.

Population Census

We used the 2020 bridged-race population estimates produced by the U.S. Census Bureau in collaboration with the National Center for Health Statistics for demographic variables.

Analysis Data Set

For approximately 10.6 million North Carolina residents, we extracted data regarding Covid-19–related vaccination history and clinical outcomes (Covid-19, hospitalization, and death) during a 9-month period (December 11, 2020, to September 8, 2021) by linking data from the NC COVID and CVMS systems (see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). Vaccination

data were available only for residents who were vaccinated in North Carolina by a North Carolina state provider or federal pharmacy provider. Covid-19 was defined as either asymptomatic or symptomatic infection with SARS-CoV-2. We used 2020 census data to determine the total number of residents in subgroups defined according to the following demographic variables: age, sex, race or ethnic group, geographic region, and county-level vaccination rate.

STATISTICAL ANALYSIS

A Cox regression model was used to evaluate vaccine effectiveness in reducing the hazard rate (i.e., current risk) of Covid-19 over time, with adjustment for confounding factors.[13-15] Time to disease was measured from the same date (December 11, 2020) for all persons in order to control for time-varying confounders (e.g., level of community transmission and prevalence of the delta variant) in comparing the incidence of Covid-19 between vaccinated and unvaccinated persons.[14,15]

The effect of a vaccine on the current risk of Covid-19 depends on the time elapsed since the first dose.[14,15] This time-varying effect is characterized by a continuous piecewise linear function of time elapsed since the first dose for the log hazard ratio,[14,15] with a change point placed at every month. A linear function on the log hazard ratio corresponds to an exponential growth or decay of the hazard ratio.[16] The piecewise linear function allows the rate of growth or decay to take a different value starting at each change point and thus provides a more accurate representation of the trajectory of vaccine effectiveness than that provided by a single linear function. The continuity at change points reduces the number of values to be estimated and yields a continuous curve of the hazard ratio. Because the hazard rate pertains to the current risk, estimation of the hazard ratio from the time of the first dose does not bias the estimation of the hazard ratio since full vaccination; rather, it enables evaluation of the vaccine effect during the ramping-up period.

The effects of one dose and two doses of BNT162b2 (30 μg per dose), one dose and two doses of mRNA-1273 (100 μg per dose), and one dose of Ad26.COV2.S (5×10^{10} viral particles) were estimated simultaneously under a single model. Demographic variables (age, sex, race or ethnic group, geographic region, and county-level vaccination rate) were included as covariates to adjust for potential confounding by individual characteristics and geographic location. The time-varying log hazard ratios for the vaccine effects were estimated by means of maximum partial likelihood.[13] The vaccine effectiveness in reducing the current risk of Covid-19 was estimated as one minus the estimated hazard ratio; corresponding 95% confidence intervals were constructed. The same approach was used to estimate the vaccine effectiveness in reducing the current risks of hospitalization and death. Details regarding the study methods are provided in the Supplementary Appendix.

RESULTS

STUDY POPULATION

The demographic characteristics of the North Carolina population, together with the vaccine uptake and clinical outcomes in the state from December 11, 2020, to September 8, 2021, are summarized in Table 1. North Carolina has a diverse population that reflects the age and sex distributions of the United States, although the percentage of Black persons is higher and the percentages of persons who identify as Hispanic and as Asian or Pacific Islander are lower than the national averages.

Vaccination rates were highest among older adults, female persons, White persons, and persons who identify as Asian or Pacific Islander. BNT162b2 was the most commonly administered vaccine, followed by mRNA-1273. For both vaccines, injection of the first dose started in mid-December of 2020, and approximately 89% of the recipients received two doses. The median time between the first and second doses was 21 days for BNT162b2 and 28 days for mRNA-1273, with 95% and 96% of the recipients, respectively, getting the second dose within a week before or after the recommended date. Ad26.COV2.S was administered to only a small percentage of the population, and it was not administered until early March of 2021.

From December 11, 2020, to September 8, 2021, a total of 812,494 cases of Covid-19 were confirmed, of which 20,232 were known to lead to hospitalization and 7461 were known to cause death. However, hospitalization status was known for only approximately 40% of Covid-19 cases and survival status for 60%. Thus, the actual numbers

Table 1. Demographic Characteristics of the North Carolina Population According to Vaccine Uptake and Clinical Outcomes from December 11, 2020, to September 8, 2021.

Characteristic	Overall	Vaccine Uptake			Clinical Outcomes		
		BNT162b2	mRNA-1273	Ad26.COV2.S	Covid-19	Hospitalization	Death
	no.	*no. (%)*			*no. of persons with event*		
All residents	10,600,823	3,363,439 (32)	2,300,890 (22)	343,138 (3)	812,494	20,232	7,461
Age group*							
12–17 yr	806,634	396,158 (49)	688 (<1)	187 (<1)	62,214	164	3
18–34 yr	2,432,304	752,181 (31)	434,225 (18)	102,557 (4)	246,853	1,281	85
35–49 yr	1,991,144	739,740 (37)	486,286 (24)	89,374 (4)	175,733	2,484	379
50–64 yr	2,056,433	780,091 (38)	645,341 (31)	108,570 (5)	152,042	5,343	1,362
≥65 yr	1,814,542	694,655 (38)	734,228 (40)	42,431 (2)	99,944	10,747	5,630
Sex							
Female	5,448,241	1,858,727 (34)	1,266,412 (23)	158,501 (3)	430,930	9,962	3,461
Male	5,152,582	1,504,712 (29)	1,034,478 (20)	184,637 (4)	381,564	10,270	4,000
Race or ethnic group							
American Indian or Alaska Native	180,238	35,929 (20)	26,849 (15)	3,731 (2)	15,777	341	117
Asian or Pacific Islander	391,163	195,587 (50)	85,201 (22)	15,278 (4)	21,746	273	106
Black	2,453,861	723,911 (30)	508,890 (21)	66,456 (3)	200,897	5,670	1,818
White	7,575,561	2,408,012 (32)	1,679,950 (22)	257,673 (3)	574,074	13,948	5,420
Hispanic ethnic group							
Hispanic	1,052,435	312,468 (30)	158,717 (15)	39,006 (4)	77,974	1,987	549
Non-Hispanic	9,548,388	3,050,971 (32)	2,142,173 (22)	304,132 (3)	734,520	18,245	6,912
Geographic region							
Coastal	2,934,844	691,142 (24)	678,413 (23)	83,241 (3)	231,384	7,233	2,296
Piedmont	6,501,788	2,447,932 (38)	1,290,465 (20)	209,191 (3)	494,599	11,221	4,233
Mountain	1,164,191	224,365 (19)	332,012 (29)	50,706 (4)	86,511	1,778	932
County-level vaccination rate							
<65%	3,265,912	612,462 (19)	772,043 (24)	76,910 (2)	270,475	8,225	3,121
65–80%	3,939,309	1,235,497 (31)	874,317 (22)	124,711 (3)	308,194	9,095	2,958
>80%	3,395,602	1,515,480 (45)	654,530 (19)	141,517 (4)	233,825	2,912	1,382
Date of first dose							
December 11 to March 31	3,270,132	1,642,459 (50)	1,505,412 (46)	122,261 (4)	141,755	3,929	1,050
April 1 to June 30	1,906,479	1,144,003 (60)	578,450 (30)	184,026 (10)	105,307	2,248	70
July 1 to September 8	830,856	576,977 (69)	217,028 (26)	36,851 (4)	40,727	935	40

* Data for the age group of less than 12 years are not shown, because persons in that age group accounted for a small number of vaccinated persons overall.

of hospitalizations and deaths were substantially higher.

VACCINE EFFECTIVENESS AGAINST COVID-19

Estimates of vaccine effectiveness in reducing the current risk of Covid-19 are shown in Figure 1A and Table 2. For the BNT162b2 two-dose regimen, vaccine effectiveness reached a peak level of 94.5% (95% confidence interval [CI], 94.1 to 94.9) at 2 months after the first dose. Effectiveness started to decline after 2 months and decreased to 66.6% (95% CI, 65.2 to 67.8) at 7 months.

For the mRNA-1273 two-dose regimen, vaccine effectiveness reached a peak level of 95.9% (95% CI, 95.5 to 96.2) at 2 months. Effectiveness started to decline after 2 months and was maintained at 80.3% (95% CI, 79.3 to 81.2) at 7 months. The difference in effectiveness between the mRNA-1273 and BNT162b2 vaccines at 4, 5, 6, 7, and 8 months was 7.4 percentage points (95% CI, 6.6 to 8.2), 7.2 percentage points (95% CI, 6.4 to 8.0), 7.5 percentage points (95% CI, 6.4 to 8.6), 13.7 percentage points (95% CI, 12.1 to 15.3), and 10.0 percentage points (95% CI, 7.3 to 12.7), respectively.

For the Ad26.COV2.S one-dose regimen, vaccine effectiveness reached a peak level of 74.8% (95% CI, 72.5 to 76.9) at 1 month. Effectiveness started to decline after 1 month and decreased to 59.4% (95% CI, 57.2 to 61.5) at 5 months. Because Ad26.COV2.S was not deployed until March 2021, the information about its effectiveness after 5 months is limited.

We performed a sensitivity analysis by placing the change points at every 2 weeks instead of every month. The results are shown in Figure S1 in the Supplementary Appendix. The patterns were similar to those observed in the main analysis (Fig. 1A). The curves were a bit less smooth, with the peak for BNT162b2 occurring at 1.5 months after the first dose, and the confidence intervals were slightly wider.

Estimates of vaccine effectiveness for different age groups are shown in Figure 2 and Table S1. For all three vaccines, the ramping-up and waning patterns were similar across age groups, but effectiveness tended to be lower among adults 65 years of age or older than in the younger age groups. For all three vaccines, the ramping-up and waning trends were also similar across subgroups defined according to other demographic variables (sex, race or ethnic group, geographic region, and county-level vaccination rate), with noticeable differences in the level of waning in some subgroups (Figs. S2 through S5).

Estimates of vaccine effectiveness according to the date of the first dose are shown in Figure 3. For each vaccine, the curves of vaccine effectiveness as a function of time since vaccination were similar among persons vaccinated on different dates. This finding suggests that waning vaccine effectiveness was caused primarily by declining immunity over time. Among early recipients of BNT162b2 and mRNA-1273 (who received

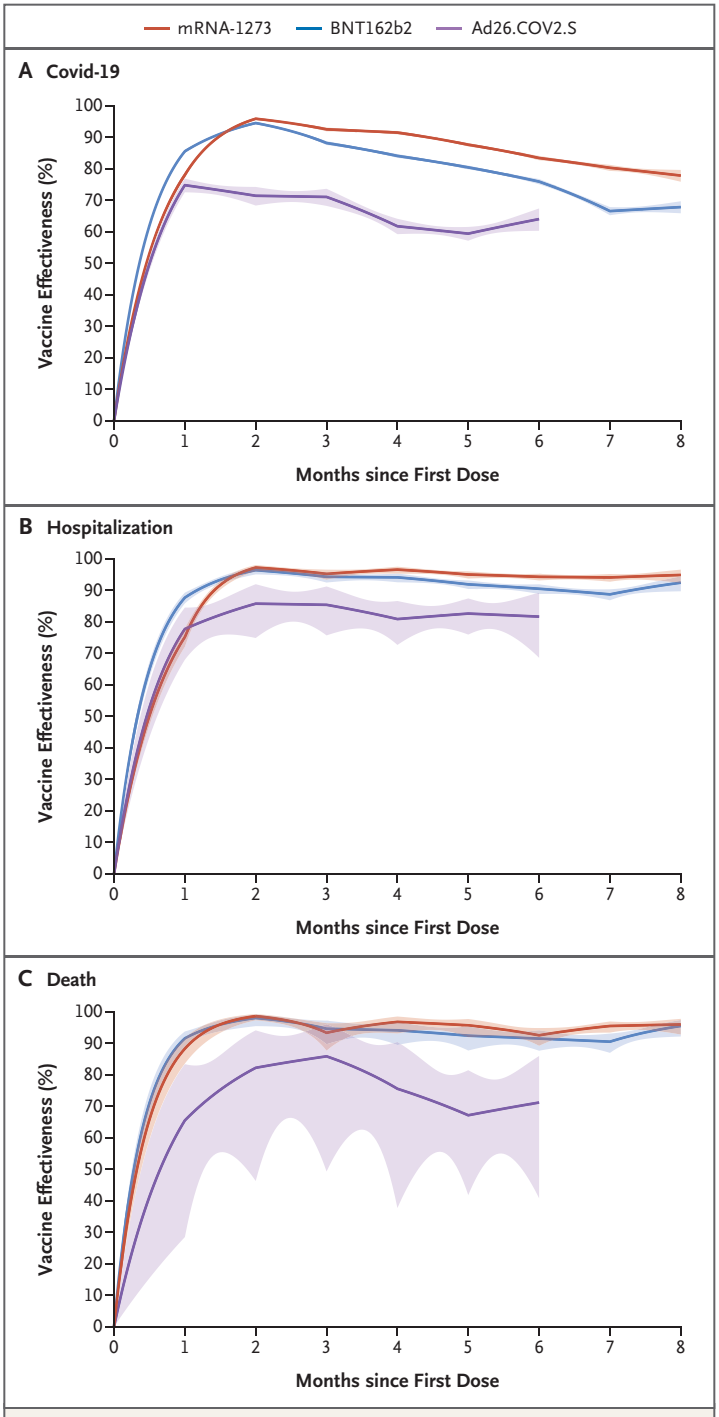

Figure 1. Effectiveness of the BNT162b2, mRNA-1273, and Ad26.COV2.S Vaccines against Covid-19, Hospitalization, and Death.

Estimates of vaccine effectiveness in reducing the current risks of Covid-19 (Panel A), hospitalization due to severe Covid-19 (Panel B), and death due to Covid-19 (Panel C) are shown for the two-dose regimens of BNT162b2 and mRNA-1273 and the one-dose regimen of Ad26.COV2.S. The shaded bands indicate 95% confidence intervals.

Table 2. Effectiveness of the BNT162b2, mRNA-1273, and Ad26.COV2.S Vaccines against Covid-19, Hospitalization, and Death, as a Function of Time Elapsed since the First Dose.*

Months since First Dose	Covid-19			Hospitalization			Death		
	BNT162b2	mRNA-1273	Ad26.COV2.S	BNT162b2	mRNA-1273	Ad26.COV2.S	BNT162b2	mRNA-1273	Ad26.COV2.S
					% (95% CI)				
1	85.5 (85.0–86.0)	78.0 (77.2–78.8)	74.8 (72.5–76.9)	87.7 (85.9–89.3)	75.2 (72.1–78.0)	77.7 (68.0–84.5)	91.6 (88.6–93.8)	88.3 (83.6–91.7)†	65.5 (28.5–83.4)
2	94.5 (94.1–94.9)	95.9 (95.5–96.2)	71.4 (68.3–74.2)	96.4 (95.1–97.4)	97.2 (96.1–98.0)	85.8 (74.9–91.9)	98.0 (95.5–99.1)	98.6 (97.3–99.3)	82.2 (46.3–94.1)
3	88.2 (87.5–88.8)	92.5 (91.9–93.1)	71.1 (68.2–73.6)	94.3 (92.5–95.7)	95.2 (93.4–96.6)	85.4 (75.7–91.2)	94.6 (89.7–97.2)	93.3 (87.7–96.4)	85.9 (49.3–96.1)
4	84.1 (83.4–84.7)	91.5 (90.9–92.0)	61.8 (59.3–64.1)	94.1 (92.6–95.4)	96.6 (95.3–97.5)	80.9 (72.7–86.6)	94.1 (89.5–96.7)	96.8 (93.1–98.5)	75.6 (37.7–90.4)
5	80.4 (79.8–81.0)	87.6 (87.1–88.2)	59.4 (57.2–61.5)	91.9 (90.4–93.1)	95.0 (93.7–96.0)	82.6 (76.0–87.4)	92.4 (87.7–95.3)	95.7 (91.9–97.7)	67.1 (41.8–81.5)
6	75.9 (75.1–76.7)	83.4 (82.7–84.1)	64.0 (60.3–67.4)	90.5 (88.8–91.9)	94.3 (93.1–95.3)	81.7 (68.6–89.3)	91.5 (87.6–94.1)	92.5 (89.2–94.9)	71.2 (40.8–86.0)
7	66.6 (65.2–67.8)	80.3 (79.3–81.2)	—	88.7 (86.9–90.3)	94.1 (92.7–95.2)	—	90.5 (87.0–93.1)	95.5 (93.4–96.9)	—
8	67.8 (65.9–69.7)	77.8 (75.9–79.6)	—	92.4 (89.7–94.4)	94.9 (92.4–96.6)	—	95.5 (92.2–97.4)	96.0 (92.8–97.8)	—

* Estimates of vaccine effectiveness and 95% confidence intervals are shown for the two-dose regimens of BNT162b2 and mRNA-1273 and the one-dose regimen of Ad26.COV2.S.
† The estimate is extrapolated from the estimates at months 0 and 2.

the first dose before March 2021), effectiveness decreased by approximately 15 and 10 percentage points, respectively, from mid-June to mid-July, when the delta variant was surging (Figs. 3 and S6). This finding suggests that the emergence of the delta variant further reduced vaccine effectiveness among those with declined vaccine-induced immunity.

VACCINE EFFECTIVENESS AGAINST HOSPITALIZATION AND DEATH

Many persons with Covid-19 were not contacted for information about clinical outcomes. Therefore, a high percentage of the data regarding hospitalization and death was missing. The percentage of persons who were reached for an interview varied over time and was generally lower during peaks of Covid-19 activity. In addition, reporting of data regarding hospitalization and death was often considerably delayed. Thus, the percentage of missing data was high in the winter and was highest during the last 2 months of the study period (Fig. S7). However, the percentage of missing records of hospitalization and death among vaccinated persons was similar to that among unvaccinated persons (Fig. S7).

We performed multiple imputation of missing data by randomly treating persons with unknown hospitalization or survival status as being hospitalized or dead in accordance with the observed rate of hospitalization or death, which depended on both the date of infection and the time since vaccination.[17] Estimates of vaccine effectiveness in reducing the current risk of hospitalization due to severe Covid-19 are shown in Figure 1B and Table 2. For the BNT162b2 two-dose regimen, vaccine effectiveness reached a peak level of 96.4% (95% CI, 95.1 to 97.4) at 2 months and was maintained at 88.7% (95% CI, 86.9 to 90.3) at 7 months. For the mRNA-1273 two-dose regimen, vaccine effectiveness reached a peak level of 97.2% (95% CI, 96.1 to 98.0) at 2 months and remained at 94.1% (95% CI, 92.7 to 95.2) at 7 months. For the Ad26.COV2.S one-dose regimen, vaccine effectiveness reached a peak level of 85.8% (95% CI, 74.9 to 91.9) at 2 months and was higher than 80% through 6 months.

For all three vaccines, the ramping-up and waning trends were similar across demographic subgroups (Figs. S8 through S12), and effectiveness was lower among adults 65 years of age or older than in the younger age groups (Fig. S8

and Table S2). A decrease in effectiveness from June to July was noted among early recipients of BNT162b2 and mRNA-1273 (Fig. S13).

Estimates of vaccine effectiveness in reducing the current risk of death due to Covid-19 are shown in Figure 1C and Table 2. For the BNT162b2 two-dose regimen, vaccine effectiveness reached 98.0% (95% CI, 95.5 to 99.1) at 2 months and remained at 90.5% (95% CI, 87.0 to 93.1) at 7 months. For the mRNA-1273 two-dose regimen, vaccine effectiveness reached 98.6% (95% CI, 97.3 to 99.3) at 2 months and remained at 95.5% (95% CI, 93.4 to 96.9) at 7 months. For the Ad26.COV2.S one-dose regimen, vaccine effectiveness reached 85.9% (95% CI, 49.3 to 96.1) at 3 months and was mostly higher than 70% through 6 months, with wide confidence intervals. For all three vaccines, effectiveness tended to be lower among adults 65 years of age or older than among adults 18 to 64 years of age (Fig. S14 and Table S3).

We performed a sensitivity analysis by increasing the event rates among vaccinated persons by 20%. The resulting estimates of vaccine effectiveness tended to be slightly lower than the original estimates (Fig. S15A). We performed another sensitivity analysis by increasing the event rates among vaccinated persons by 50%, and the resulting effectiveness estimates remained high (Fig. S15B).

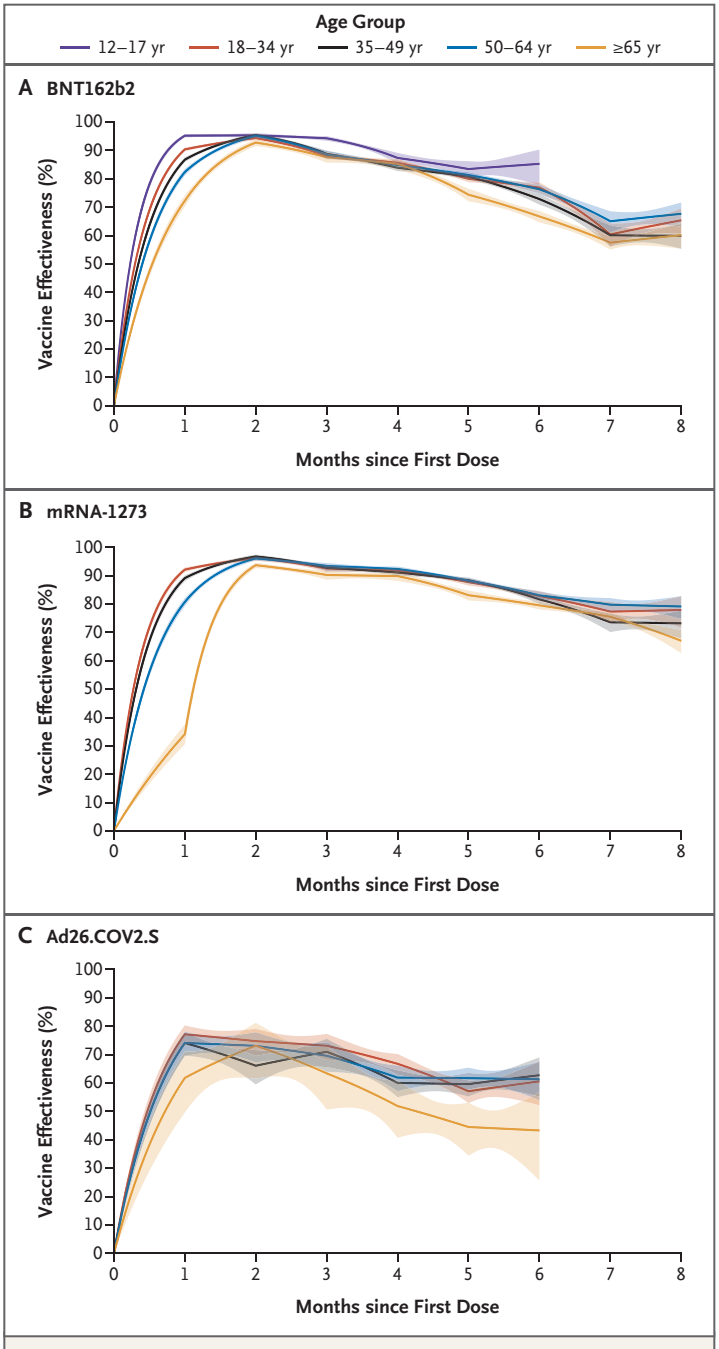

Figure 2. Effectiveness of the BNT162b2, mRNA-1273, and Ad26.COV2.S Vaccines against Covid-19 According to Age Group.

Estimates of vaccine effectiveness in reducing the current risk of Covid-19 are shown for the two-dose regimens of BNT162b2 (Panel A) and mRNA-1273 (Panel B) and the one-dose regimen of Ad26.COV2.S (Panel C). The shaded bands indicate 95% confidence intervals.

DISCUSSION

The estimates of vaccine effectiveness from this study are consistent with and complement the estimates of vaccine efficacy from phase 3 trials.[1-3,18,19] Specifically, the estimated peak levels for the three vaccines in this study are similar to those in phase 3 trials, although phase 3 trials were not powered to determine when the peak occurs. The large sample size of this study allowed us to pinpoint the timing of the peak. The estimates of long-term vaccine effectiveness against Covid-19 shown in this study are lower than results based on limited phase 3 trial data[18,19]; however, our study included both symptomatic and asymptomatic infections, and vaccine effectiveness against asymptomatic infection is expected to be lower than that against symptomatic infection, which was the primary end point in the phase 3 trials.

Our results showed that the effectiveness of the two messenger RNA (mRNA) vaccines — BNT162b2 and mRNA-1273 — was very high and durable against hospitalization and death and that mRNA-1273 was somewhat more effective than

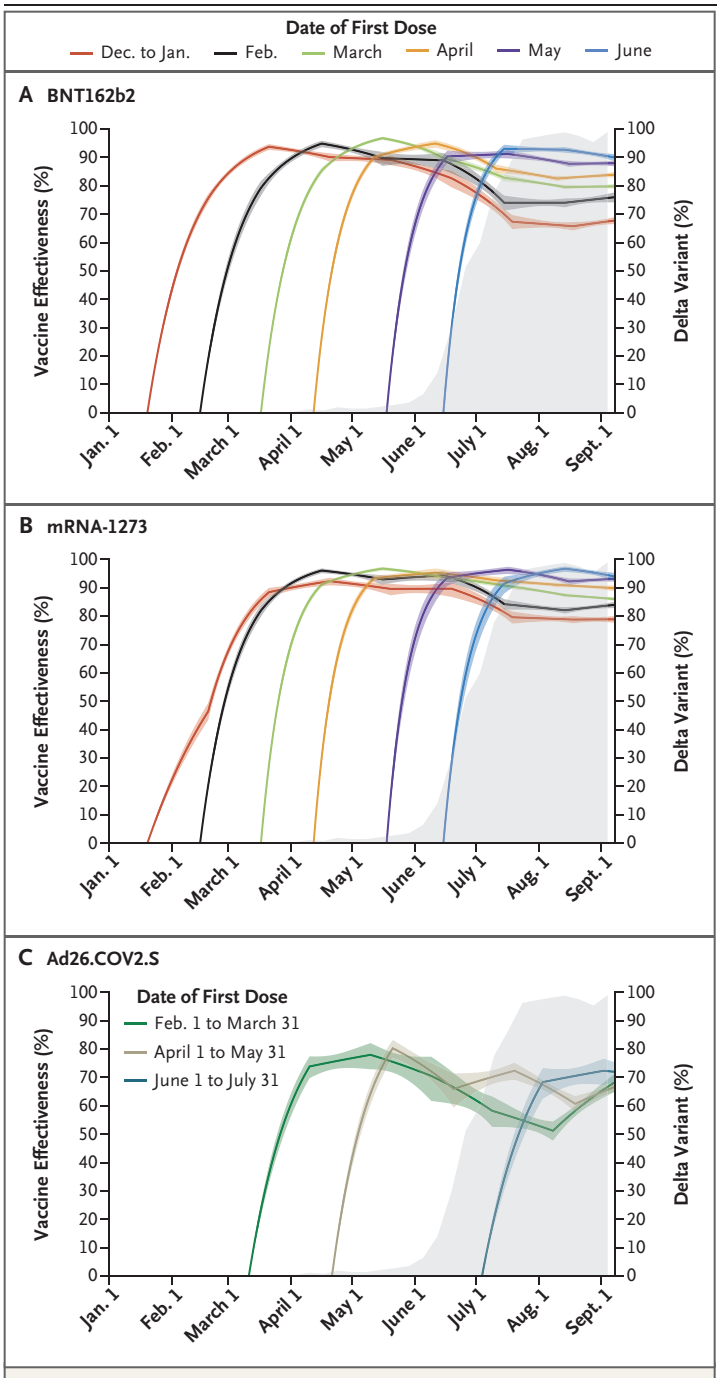

Figure 3. Effectiveness of the BNT162b2, mRNA-1273, and Ad26.COV2.S Vaccines against Covid-19 According to Date of First Dose.

Estimates of vaccine effectiveness in reducing the current risk of Covid-19 are shown for the two-dose regimens of BNT162b2 (Panel A) and mRNA-1273 (Panel B) and the one-dose regimen of Ad26.COV2.S (Panel C), alongside the prevalence of the B.1.617.2 (delta) variant among all cases of Covid-19 (gray shaded area). The shaded bands indicate 95% confidence intervals.

BNT162b2 against Covid-19. Note that BNT162b2 was given at a lower dose than mRNA-1273 (30 μg per injection vs. 100 μg per injection). In addition, Ad26.COV2.S offered a high level of protection against hospitalization and death, and its effectiveness against Covid-19 reached a peak level similar to that of the two mRNA vaccines 1 month after vaccination and then started to decline.

A recent study from Israel showed that the rate of Covid-19 during the period of July 11 to 31, 2021, among persons who had become fully vaccinated with BNT162b2 in January was 1.6 times as high as the rate among persons who had become fully vaccinated with BNT162b2 in March, and the rate ratio for severe disease was more than 1.8.[11] These differences seem more substantial than those observed in the main analysis of our study; however, when a vaccine is highly effective, comparison of the event rates between persons vaccinated in two different time periods conveys a greater sense of waning than comparison of the vaccine effectiveness. Indeed, in our study, the rate of Covid-19 during the period of July 11 to 31, 2021, among persons who had received the second dose of BNT162b2 in January was 1.5 times as high as the rate among persons who had received the second dose of BNT162b2 in March; the rate ratio for hospitalization could not be calculated because of small numbers and incomplete data. A recent study from the state of New York compared vaccine effectiveness in May, June, July, and August of 2021 among persons who were vaccinated in January–February, March, and April of 2021.[12] The life-table method was used to estimate hazard rates over 7-day intervals. The resulting estimates of vaccine effectiveness are unstable, and the confidence intervals are too wide to lead to firm conclusions.

Our study was observational and thus was limited by confounding bias. We adjusted for measured confounders (age, sex, race or ethnic group, geographic region, and county-level vaccination rate). Of greater importance, we measured the time to disease occurrence from the start of the study in order to compare disease incidence between vaccinated and unvaccinated persons on the same date, thus avoiding confounding due to time trends (e.g., level of community transmission and prevalence of new variants). However, persons who choose not to be vaccinated may differ from those who choose to be vaccinated in terms of

their use of other prevention measures. In addition, persons who have Covid-19 symptoms may delay vaccination. It would be difficult to quantify the potential bias caused by these confounding factors.

This study included data regarding vaccination history only for persons who were vaccinated in North Carolina by a North Carolina state provider or federal pharmacy provider. Recipient-level vaccination data for North Carolina residents who were vaccinated outside North Carolina and for residents who were vaccinated through a federal entity (Department of Defense, Veterans Health Administration, Indian Health Service, or Federal Bureau of Prisons) are not available through CVMS and therefore were not included in the analysis. Those data represent less than 5% of total vaccine administrations in North Carolina.

Routinely linked communicable-disease and vaccine-registry data from comprehensive statewide surveillance systems are useful for studying vaccine effectiveness. The methods developed for this study can be applied to surveillance-linked laboratory and vaccination data from other states. By combining data from multiple states, we would be able to gain a more comprehensive understanding of vaccine effectiveness in the United States. With additional follow-up data, we would be able to evaluate not only the effectiveness of the original vaccine series beyond 9 months but also the effectiveness of the booster programs and the need for additional boosters.

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