Protection of mRNA vaccines against hospitalized COVID-19 in adults over the first year following authorization in the United States

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For the Influenza and Other Viruses in the Acutely Ill (IVY) Network**

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Short Title: COVID-19 vaccine effectiveness over time

ABSTRACT

Background: COVID-19 mRNA vaccines were authorized in the United States in December 2020. Although vaccine effectiveness (VE) against mild infection declines markedly after several months, limited understanding exists on the long-term durability of protection against COVID-19-associated hospitalization.

Methods: Case control analysis of adults (≥18 years) hospitalized at 21 hospitals in 18 states March 11 – December 15, 2021, including COVID-19 case patients and RT-PCR-negative controls. We included adults who were unvaccinated or vaccinated with two doses of a mRNA vaccine before the date of illness onset. VE over time was assessed using logistic regression comparing odds of vaccination in cases versus controls, adjusting for confounders. Models included dichotomous time (<180 vs ≥180 days since dose two) and continuous time modeled using restricted cubic splines.

Results: 10,078 patients were included, 4906 cases (23% vaccinated) and 5172 controls (62% vaccinated). Median age was 60 years (IQR 46–70), 56% were non-Hispanic White, and 81% had ≥1 medical condition. Among immunocompetent adults, VE <180 days was 90% (95%CI: 88–91) vs 82% (95%CI: 79–85) at ≥180 days (p<0.001). VE declined for Pfizer-BioNTech (88% to 79%, p<0.001) and Moderna (93% to 87%, p<0.001) products, for younger adults (18-64 years) [91% to 87%, p=0.005], and for adults ≥65 years of age (87% to 78%, p<0.001). In models using restricted cubic splines, similar changes were observed.

Conclusion: In a period largely pre-dating Omicron variant circulation, effectiveness of two mRNA doses against COVID-19-associated hospitalization was largely sustained through 9 months.

Key Words:
COVID-19; duration of protection; waning; vaccine effectiveness; mRNA

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic led to an estimated 5.4 million deaths worldwide through December 2021 [1]. Highly effective vaccines are available, and vaccination is the best tool to control the impact of the pandemic [2, 3]. In the United States, three licensed vaccines are available, with most vaccinated persons receiving messenger RNA (mRNA) COVID-19 vaccine products including mRNA-1273 (from Moderna) and BNT162b2 (from Pfizer-BioNTech) [4]. Vaccination has reduced the burden of COVID-19 including COVID-19-associated deaths in the U.S. [5, 6], with most severe COVID-19 illnesses and deaths occurring among unvaccinated persons [7, 8].

In countries with higher vaccination coverage, reductions in vaccine effectiveness (VE) with passage of time prompted booster recommendations for COVID-19 vaccines [9]. In these vaccinated populations, surges of COVID-19 complicate the understanding of the protective effect of vaccines and policy discussions for several reasons. First, with increasing time since vaccination, protection has varied by disease severity, with more sustained vaccine protection against severe disease as compared with mild infections [10, 11]. These infections in vaccinated individuals could be due to waning of antibodies [12, 13], particularly in the mucosal compartments at the site of infection, or from emergence of SARS-CoV-2 variants that might escape immune protection. In contrast, durable memory B cell and T cell responses might provide sustained protection against more severe disease [14], possibly including heterotypic protection against new variants. Second, protection may differ by underlying conditions such as immunosuppression [15], vaccine product [16, 17], and number of doses received [18]. Thus, as the pandemic continues to evolve, disentangling factors of waning immunity, viral evasion of immunity, number of doses and type of vaccine, and host immune responses have become increasingly complex. Ongoing real-world VE studies in large, diverse populations can inform vaccination program goals in terms of understanding of protection provided for different levels of disease severity, populations in

whom booster doses may be most beneficial for the prevention of severe outcomes and timing of booster doses, and the need for potential antigen updates in vaccines.

The Centers for Disease Control and Prevention (CDC) collaborates with the Influenza and Other Viruses in the Acutely Ill (IVY) Network to monitor the effectiveness of vaccines for the prevention of COVID-19-associated hospitalizations among U.S. adults [3, 16]. In this report, we evaluate the duration of 2-dose mRNA vaccine protection against COVID-19 hospitalizations during the first year of the U.S. vaccination program. Our primary goal was to examine VE over time by host factors such as age and underlying conditions, vaccine product, and immunosuppression status to evaluate the durability of vaccine protection to inform future vaccine strategies.

METHODS

We monitor the effectiveness of COVID-19 vaccines for the prevention of COVID-19 hospitalization among U.S. adults (≥18 years of age) by enrolling adults at 21 U.S. medical centers. We assessed the effectiveness of the mRNA vaccines over time in patients admitted March 11 through December 15, 2021 using a case-control design. Interim durability estimates including IVY Network enrollments through July 14, 2021 were previously published (including 3089 hospitalized adults, with a median of 65 days between receipt of dose 2 and illness onset among vaccinated patients) [19]; this analysis adds five additional months of enrollment data including a longer duration of follow-up since vaccination during a period when the SARS-CoV-2 Delta variant predominated.

We considered immunocompetent and immunocompromised patients separately because of variation in immune responses to COVID-19 vaccination in these patients.[15]. Immunocompromising conditions were defined as having one or more of the following: active solid organ cancer (defined as treatment for the cancer or newly diagnosed cancer in the past 6 months), active hematologic cancer, HIV infection with or without AIDS, congenital immunodeficiency syndrome, previous splenectomy, previous solid

organ transplant, active immunosuppressive medication use, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, scleroderma, or inflammatory bowel disease. Enrollment methods have previously been described [3, 7]. In brief, COVID-19 case patients had COVID-19-like illness (CLI) and tested positive for SAR-CoV-2 by molecular or antigen test within 10 days of illness onset. Two control groups of hospitalized adults without COVID-19 were included: (1) a "test-negative" control group comprised of patients hospitalized with CLI who tested negative for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) and (2) a "syndrome-negative" control group comprised of patients hospitalized without CLI who tested negative for SARS-CoV-2 by RT-PCR. VE using individual control groups was highly similar, and therefore patients from both groups were combined into a single control group. Case or control status was determined using SARS-CoV-2 clinical testing results and results from central RT-PCR testing of upper respiratory specimens collected at enrollment and tested at Vanderbilt University Medical Center (Nashville, Tennessee). Patients enrolled as test-negative controls who subsequently tested positive for SARS-CoV-2 were reassigned as a COVID-19 case-patient and syndrome-negative controls with a subsequent positive SARS-CoV-2 test were excluded from the analysis.

COVID-19 vaccination status and vaccine product information were determined through self-report during enrollment interviews with patients or their proxies and systematic review of source documentation including hospital electronic medical records, state vaccine registry searches, and vaccination record cards. Patients were considered vaccinated for this analysis if two doses of a single mRNA vaccine product were documented or self-reported (with date and location) ≥14 days before a reference date, defined as the date of symptom onset for cases and test-negative controls or five days prior to hospital admission for syndrome-negative controls. If no COVID-19 vaccine was received prior to the reference date, patients were considered unvaccinated. Patients who received 1 or more doses of a mRNA vaccine but did not meet study criteria for full vaccination, who received mixed vaccine products,

or who received a non-mRNA vaccine were excluded, as well as patients who received more than two doses of a mRNA vaccine with the third dose received ≥7 days before illness onset.

Patients were classified as being in a period of higher proportions of lineages other than Delta (pre-Delta) period if their admission date was before July 1st 2021 [4]. Otherwise, patients with an admission date on or after July 1st, 2021 were classified as being in a period of higher B.1.617.2 and AY lineages (Delta period). Information on patients' age, sex, self-reported race and ethnicity, and preexisting chronic medical conditions were obtained through electronic medical record review and structured enrollment interviews.

Logistic regression models were used to estimate VE by time since vaccination with different models treating time as binary (<180 days vs ≥180 days between second dose and reference date) and as continuous (applied a restricted cubic spline with number of knots determined by the lowest AIC of the regression model tested with 3-7 knots). Briefly, we applied a spline to the daily time term due to the non-linear nature of VE over time; in other words, the use of splines allowed the waning speed to change over time opposed to a constant decline. Each logistic regression model used COVID-19 case status as the outcome and vaccination status (vaccinated vs unvaccinated) as the predictor along with the time since vaccination term (binary or continuous). Models included additional covariates for calendar date of admission (in biweekly intervals), age (continuous years), sex, self-reported race and ethnicity, presence of underlying chronic conditions, immunocompromised status, and US Health and Human Services region of the admitting hospital. Unvaccinated patients were assigned a reference value of zero days since vaccination. In binary time models, VE was estimated using logistic regression comparing odds of case vs control outcome by a primary predictor of vaccination status (vaccinated <180 days before symptom onset, vaccinated ≥180 days since symptom onset, or unvaccinated), using the equation $VE = (1 - aOR) \times 100$. In continuous time models, VE was calculated at each time since vaccination *t* as $VE(t) = (1 - aOR(t)) \times 100$, where aOR(t) is the estimated odds ratio of being a case

patient for vaccinated patients at *t* days since vaccination compared to an unvaccinated patient at 0 days adjusted for the specified covariates. 95% confidence intervals (CI) for these VE curves were obtained using bootstrapping with 1000 replicates. Interaction terms were introduced to evaluate VE over time stratified by characteristics of interests including age group (18–64 years or ≥65 years), underlying chronic medical conditions (0 vs ≥1), vaccine product received (Pfizer BioNTech vs Moderna), and baseline immunocompromising conditions. An additional model limited to patients with admission date on or after July 1st, 2021 was conducted to estimate VE over the Delta period. Separate models were constructed for immunocompetent and immunosuppressed participants due to known effect modification of VE by immune function status [15].

VE across binary time since vaccination groups was compared with likelihood ratio chi-squared tests. P-values <0.05 were considered statistically significant. This activity was conducted as a public health surveillance activity, with waiver of informed consent.

RESULTS

Of 12,513 patients enrolled through December 15, 2021, 2435 were excluded (1312 who were not vaccinated with 2 doses of a mRNA vaccine or received a third dose; 606 who received a non-mRNA vaccine or mixed products; and 517 who met other exclusion criteria). Of 10,078 patients included in the analysis, 4906 (49%) were COVID-19 case patients and 5172 (51%) were COVID-19-negative controls (Table 1). Among 4906 cases, 1119 (23%) were vaccinated and, among 5172 controls, 3229 (62%) were vaccinated. Overall, median age was 60 years (IQR: 46 – 70), 5675 (56%) were non-Hispanic White, 2198 (22%) non-Hispanic Black, and 1589 (16%) Hispanic of any race, 8203 (81%) had one or more chronic medical conditions, and 1940 (19%) had an immunocompromising condition. COVID-19 case patients were younger on average than controls (median 57 vs 62 years; p<0.001), were less likely to report having prior laboratory confirmed infection with SARS-CoV-2 (3% vs 9%; p<0.001), and, among those

who were vaccinated, had a longer median time since receiving the second vaccine dose (median 163 vs 127 days, p<0.001). Among 4862 (99%) COVID-19 case-patients with hospital outcomes, 538 (11%) died within 28 days of admission, 1919 (39%) were admitted to the intensive care unit, and the median length of stay among those who survived and were discharged by day 28 (n = 3782) was 6 (IQR 3 – 10) days.

Overall, adjusted VE among patients with immunocompromising conditions was 63% [95% CI: 55 – 69], and decreased from <180 days (65% [95%CI: 57 – 72]) to ≥180 days (53% [95%CI: 38 – 65]) after vaccine dose two (p=0.04) [Figure 1]. VE among immunocompetent individuals decreased between <180 days (90% [95% CI: 88 – 91]) at a median of 108 days (interquartile range [IQR]: 65-143) and ≥180 days (82% [95% CI: 79 – 85]) at a median of 215 days (IQR: 197-240) after the second vaccine dose (p<0.001). Restricting to the period of predominant SARS-CoV-2 Delta circulation, accounting for 72% of patient enrollments, results were largely similar with an estimated VE of 90% [95%CI: 88 – 91] at <180 days versus 83% [95%CI: 80 – 86] at ≥180 days (p<0.001). Among immunocompetent adults, VE was higher at <180 days compared to ≥180 days across multiple subgroups (all p<0.05), including adults aged 18-64 years (91% [95%CI: 90 – 93] vs 87% [95%CI: 83 – 90]; p=0.005); adults ≥65 years of age (87% [95%CI: 84 – 89] vs 78% [95%CI: 72 – 82]; p<0.001); the Pfizer-BioNTech product (88% [95%CI: 86 – 90] vs 79% [95%CI: 74 – 83]; p<0.001); the Moderna product (93% [95%CI: 91 – 94] vs 87% [95%CI: 83 – 90]; p<0.001); those with no underlying chronic medical conditions (97% [95%CI: 96 – 98] vs 90% [95%CI: 84 – 94]; p<0.001); and those with ≥1 underlying condition (88% [95%CI: 86 – 89] vs 80% [95%CI: 76 – 84]; p<0.001) [Figure 1].

Next, we looked at VE over continuous time. The continuous time since vaccination models performed best, based on the lowest AIC of the overall model, using a restricted cubic spline term with 5 knots. Standard quantiles for the cubic spline for time since vaccination of 0.05, 0.275, 0.50, 0.775, and 0.95 (at 31, 91, 140, 187, and 253 days since vaccination) were used. In immunocompetent patients, VE was 90%

initially (at 14 days since vaccination), increased to a maximum of 93% after 75 days, and then decreased to 80% after 270 days (Figure 2), with time since vaccination being a significant factor in estimating VE ($p<0.001$). Among immunocompetent adults, VE estimates similarly varied by time within subgroups of interest. For the Pfizer-BioNTech vaccine, VE peaked at 92% after 74 days and decreased to 75% at 270 days, and for the Moderna product VE peaked at 94% after 83 days and decreased to 86% after 270 days [Figure 3], with time from vaccination being significant in each group ($p<0.001$). For those aged 18-64, VE peaked at 94% after 84 days and decreased to a minimum of 86% at 198 days, and for those 65 or older VE peaked at 92% initially at 14 days and decreased to 73% after 270 days [Figure 4], with time from vaccination being significant in each group ($p<0.001$). Models testing additional interactions also showed a change in VE over time for both the group with no underlying conditions and those with ≥1 underlying condition (Supplementary Figure 1) and for those in the Delta period (Supplementary Figure 2). Immunosuppressed individuals showed overall lower VE compared to immunocompetent patients over time (Supplementary Figure 3).

DISCUSSION

In this multicenter evaluation across 18 states over the first year following COVID-19 vaccine introduction, we found that vaccination with two doses of an mRNA product provided protection against COVID-19 hospitalization prior to predominant Omicron variant and subvariant circulation. Effectiveness was generally sustained at ≥80% over a period of 270 days with some gradual decline after peaking 2-3 months after the second vaccine dose. This pattern of protection was similar across subgroups, such as by vaccine product. Notably, overall protection was lower for older adults (≥65 years of age) compared to young adults (18-64 years of age) and was modestly lower after 180 days (87% vs 78%), highlighting the importance of additional vaccine doses in older adults who are at increased risk of severe COVID-19 illness. Both mRNA vaccine products provided a high level of protection, with modestly higher VE observed for the Moderna compared to the Pfizer-BioNTech vaccine [16, 17]

Findings from our analysis are consistent with published studies that have shown consistently high and generally sustained protection from COVID-19 mRNA vaccines against severe outcomes [7, 10]. Almost three-quarters of COVID-19 cases occurred during a period in which the SARS-CoV-2 Delta variant accounted for most infections in the U.S. However, the surveillance period pre-dated more recent circulation of the SARS-CoV-2 Omicron variant, which has greater immune escape corresponding with lower vaccine protection [20, 21]. In contrast to protection against severe disease, studies show that protection against milder infection decreases faster with time since vaccination [10]. This could be related to waning antibodies or escape from neutralizing antibody protection for new SARS-CoV-2 variants that circulated after mRNA vaccine introduction [22]. Varied protection by outcome is consistent with the nature of immunity against respiratory infections, including influenza [23]. With respiratory infections, mechanisms of immunity are complex and involve mucosal and humoral compartments [23]. Immunity can be time-varying with shorter duration of protection at the mucosal surfaces, which might lead to breakthrough infections after primary infection or vaccination. However, recall of memory responses can prevent severe disease, or attenuate severe disease in immunized persons with breakthrough infections.

Our findings might contribute to future discussions around goals of the COVID-19 vaccination program and booster doses, especially as recurrent surges in infections continue to occur either due to declining immunity or emergence of variants that escape immunity, such as Omicron [24]. Recommendations for additional COVID-19 vaccine doses have been implemented in several countries [25, 26]. These decisions were initially driven by findings of suboptimal protection in immunosuppressed persons and declining protection against mild to moderate infection over time or with emerging variants. Recent increases in SARS-CoV-2 incidence were caused almost exclusively by the Omicron variant and subvariants which evade vaccine-associated immunity to a greater extent than prior circulating variants [21, 27]. Although additional vaccine doses diversify protection against more divergent variants from the ancestral strain

(WA1/2020) targeted by current vaccines, these benefits may be relatively short-lived compared to conserved protection we observed against previously circulating variants [26, 28]. Strategies used for influenza vaccination, including international surveillance with antigenic and genetic characterization of viruses and/or forecasting coupled with periodic updates in vaccine antigens and/or multivalent vaccines, may be a long-term strategy to durably reduce the impact of severe COVID-19 as SARS-CoV-2 continues to circulate globally. However, challenges remain in predicting new SARS-CoV-2 variants.

Our report has several limitations. We focused on hospitalized outcomes only. We did not include adults who received more than 2 doses of an mRNA vaccine, first recommended for individuals with immunocompromising conditions in August 2021 [29] and in the general adult population in November 2021 [9]. We did not include adults who received mixed vaccine products due to a limited number of patients with heterologous vaccination. These data predated more recent predominance of the SARS-CoV-2 Omicron variant. We also could not control for some potential time-varying confounders such as varying force of infection due to factors such as changes in mitigation measures. Although this analysis included hospitalized adults from 18 geographically and demographically diverse states, patients may not have been fully representative of the US adult population. In models evaluating patients with immunocompromising conditions, diverse immunocompromising conditions associated with variable degrees of immunosuppression and potentially with durability of vaccine protection were combined. Lastly, a high proportion of these hospitalized adults had multiple chronic medical conditions, thus reducing the generalizability to other populations with lower burden of chronic medical conditions.

Conclusions

In this multi-center US study, we found high and largely sustained protection against COVID-19 following receipt of two doses of mRNA vaccine in medically complex hospitalized patients. These findings reinforce that even with increasing infections in vaccinated populations, vaccination continued to

provide sustained protection against severe COVID-19 resulting in hospitalization. With recurrent surges in infection and emergence of SARS-CoV-2 variants with greater immune evasion [20, 30], ongoing monitoring of VE in hospitalized patients can inform prioritizing certain populations with additional vaccine doses or development of vaccines with updated antigens.

Notes:

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Table 1. Characteristics of COVID-19 case patients and controls without COVID-19 enrolled in vaccine effectiveness analysis — 21 hospitals* in 18 US states, March–December 2021.

Characteristic (count, %)	**Overall**	**Controls**	**COVID-19 Cases**
Sample Size	10078	5172	4906
Vaccinated with 2 doses[†]	4348 (43.1)	3229 (62.4)	1119 (22.8)
Vaccine Product			
Moderna	1777 (40.9)	1389 (43.0)	388 (34.7)
Pfizer-BioNTech	2571 (59.1)	1840 (57.0)	731 (65.3)
Days from second dose to onset (Amongst Vaccinated), median (IQR)	139 [84, 190]	127 [75, 182]	163 [121, 206.5]
Time from second dose to onset			
Less than 180 days	3042 (70.0)	2390 (74.0)	652 (58.3)
180 days or more	1306 (30.0)	839 (26.0)	467 (41.7)
Time Period			
Pre-Delta variant period (March-June)	2800 (27.8)	1700 (32.9)	1100 (22.4)
Delta variant period (July-December)	7278 (72.2)	3472 (67.1)	3806 (77.6)
Age in years, median (IQR)	60 [46, 70]	62 [49, 72]	57 [43, 68]
65 years or older	3837 (38.1)	2271 (43.9)	1566 (31.9)
Female	4870 (48.3)	2587 (50.0)	2283 (46.5)
Race/Ethnicity[§]			
White, non-Hispanic	5675 (56.3)	3091 (59.8)	2584 (52.7)
Black, non-Hispanic	2198 (21.8)	1111 (21.5)	1087 (22.2)
Any race, Hispanic	1589 (15.8)	681 (13.2)	908 (18.5)
All other races, non-Hispanic	457 (4.5)	222 (4.3)	235 (4.8)
Unknown	159 (1.6)	67 (1.3)	92 (1.9)
U.S. Census region[¶]			
Northeast	1537 (15.2)	749 (14.5)	786 (16.0)
South	3967 (39.4)	2050 (39.6)	1917 (39.1)
Midwest	2435 (24.2)	1230 (23.8)	1205 (24.6)
West	2141 (21.2)	1143 (22.1)	998 (20.3)
Residence in long-term care facility [missing 341] **	421 (4.3)	282 (5.6)	139 (2.9)
Employed [missing 1786]	2804 (33.8)	1123 (25.7)	1681 (42.9)
Health care worker	388 (4.7)	178 (4.1)	210 (5.4)
Attended some college or more [missing 3049]	3585 (51.0)	1983 (52.1)	1602 (49.7)
≥1 hospital admission in past year [missing 757]	3904 (41.9)	2643 (55.0)	1261 (27.9)
Self-reported prior laboratory-confirmed SARS-CoV-2 infection [missing 1]	626 (6.2)	475 (9.2)	151 (3.1)
Number of categories of underlying			

medical conditions [††]			
0 categories of underlying conditions	1875 (18.6)	567 (11.0)	1308 (26.7)
≥1 category of underlying conditions	8203 (81.4)	4605 (89.0)	3598 (73.3)
Obese by body-mass index	4779 (47.7)	2103 (40.9)	2676 (55.0)
Immunosuppression Status[§§]			
Immunocompetent	8138 (80.8)	4011 (77.6)	4127 (84.1)
Immunocompromised	1940 (19.2)	1161 (22.4)	779 (15.9)

* Hospitals by region included Northeast: Baystate Medical Center (Springfield, Massachusetts), Beth Israel Deaconess Medical Center (Boston, Massachusetts), Montefiore Medical Center (Bronx, New York); South: Vanderbilt University Medical Center (Nashville, Tennessee), University of Miami Medical Center (Miami, Florida), Emory University Medical Center (Atlanta, Georgia), Johns Hopkins Hospital (Baltimore, Maryland), Wake Forest University Baptist Medical Center (Winston-Salem, North Carolina), Baylor Scott & White Medical Center (Temple, Texas); Midwest: University of Iowa Hospitals and Clinics (Iowa City, Iowa), University of Michigan Hospital (Ann Arbor, Michigan), Hennepin County Medical Center (Minneapolis, Minnesota), Barnes-Jewish Hospital (St. Louis, Missouri), Cleveland Clinic (Cleveland, Ohio), Ohio State University Wexner Medical Center (Columbus, Ohio); West: Stanford University Medical Center (Stanford, California), UCLA Medical Center (Los Angeles, California), UCHealth University of Colorado Hospital (Aurora, Colorado), Oregon Health & Science University Hospital (Portland, Oregon), Intermountain Medical Center (Murray, Utah), University of Washington (Seattle, Washington).

[†] "Fully vaccinated" with mRNA COVID-19 vaccines defined as ≥14 days from dose 2.

[§] Racial and ethnic groups were reported by the patient or proxy.

[¶] Long-term care facility included reporting living in a nursing home, assisted living home, or rehabilitation hospital or other subacute or chronic facility before the hospital admission.

** Underlying medical condition categories were obtained through medical chart review by trained personnel. Underlying conditions were defined as having a chronic condition within one or more of the

following condition categories: cardiovascular disease, neurologic disease, pulmonary disease, gastrointestinal disease, endocrine disease, renal disease, and hematologic disease.

[††] Immunocompromising conditions included having one or more of the following: active solid organ cancer (active cancer defined as treatment for the cancer or newly diagnosed cancer in the past 6 months), active hematologic cancer (such as leukemia, lymphoma, or myeloma), HIV infection without AIDS, AIDS, congenital immunodeficiency syndrome, previous splenectomy, previous solid organ transplant, immunosuppressive medication, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, scleroderma, or inflammatory bowel disease, including Crohn's disease or ulcerative colitis.

Figure 1. Adjusted vaccine effectiveness* against COVID-19 among hospitalized adults, by subgroup[†,§] and time interval between vaccination and illness onset

***Adjusted Vaccine effectiveness (VE) was estimated using logistic regression comparing odds of case vs a control outcome by a primary predictor of vaccination status (vaccinated less than 180 days before symptom onset, vaccinated 180 days or more since symptom onset, or unvaccinated), using the equation VE = 100 × (1 – odds ratio). All models adjusted for additional covariates of date of hospital admission (biweekly intervals), US Department of Health and Human Services region of hospital, age (continuous), sex, and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic of any race, non-Hispanic Other, or unknown), and number of condition categories (0 vs 1 or more underlying conditions). All models excluded immunocompromised individuals except for that comparing VE of immunocompetent and immunocompromised individuals. The model of VE for those with no underlying conditions and those with underlying conditions included an interaction term between underlying conditions and vaccination status. Similarly, each model of VE for Pfizer-BioNTech vs Moderna, 18–64-year-olds vs those aged 65 and older, and immunocompetent vs immunocompromised individuals each included an additional covariate for vaccine product, age group, and immunosuppression status respectively as well as an interaction between this factor and vaccination status. VE for delta period was restricted only to patients with reference dates on or after July 1st, 2021, representing a period of primarily Delta-variant. Error bars represent 95% confidence intervals.

[†] Immunocompromising conditions included having one or more of the following: active solid organ cancer (active cancer defined as treatment for the cancer or newly diagnosed cancer in the past 6 months), active hematologic cancer (such as leukemia, lymphoma, or myeloma), HIV infection without AIDS, AIDS, congenital immunodeficiency syndrome, previous splenectomy, previous solid organ transplant, immunosuppressive medication, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, scleroderma, or inflammatory bowel disease, including Crohn's disease or ulcerative colitis.

[§] Underlying conditions were defined as having a chronic condition within one or more of the following condition categories: cardiovascular disease, neurologic disease, pulmonary disease, gastrointestinal disease, endocrine disease, renal disease, and hematologic disease.

Figure 2. Vaccine effectiveness* against COVID-19 by time since vaccination[†] and histogram of counts of vaccinated cases and controls by time since vaccination in immunocompetent participants

***** Adjusted Vaccine Effectiveness was calculated at each time since vaccination t as $VE(t) = (1 - \mathrm{aOR}(t)) \times 100$ where $\mathrm{aOR}(t)$ is the estimated odds ratio of being a case patient for vaccinated patients at *t* days since vaccination compared to an unvaccinated patient at 0 days adjusted for the specified covariates. The model was adjusted for additional covariates of date of hospital admission (biweekly intervals), US Department of Health and Human Services region of hospital, age (continuous), sex, and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic of any race, non-Hispanic Other, or unknown), and number of condition categories (0 vs 1 or more underlying conditions). Immunocompromised individuals were excluded from this model. Dotted lines represent 95% confidence intervals.

[†] Time since vaccination is calculated as time between reference date (date of illness onset or five days before hospital admission date for syndrome negative group) and date of second vaccine dose. Unvaccinated individuals were given a time since vaccination of 0 days.

Figure 3. Vaccine effectiveness* against COVID-19 by time since vaccination and vaccine product. Histogram of counts of vaccinated cases and controls by time since vaccination in immunocompetent participants

* Adjusted Vaccine Effectiveness was calculated using a similar logistic regression model to the overall model, with additional interaction terms for vaccine product by vaccine status and time since vaccination. Immunocompromised individuals were excluded from this model. Dotted lines represent 95% confidence intervals.

Figure 4. Vaccine effectiveness* against COVID-19 by time since vaccination† and age group. Histogram of counts of vaccinated cases and controls by time since vaccination in immunocompetent participants

* Adjusted Vaccine Effectiveness was calculated using a similar logistic regression model to the overall model, with additional interaction terms for age group by vaccine status and time since vaccination. Immunocompromised individuals were excluded from this model. Dotted lines represent 95% confidence intervals.

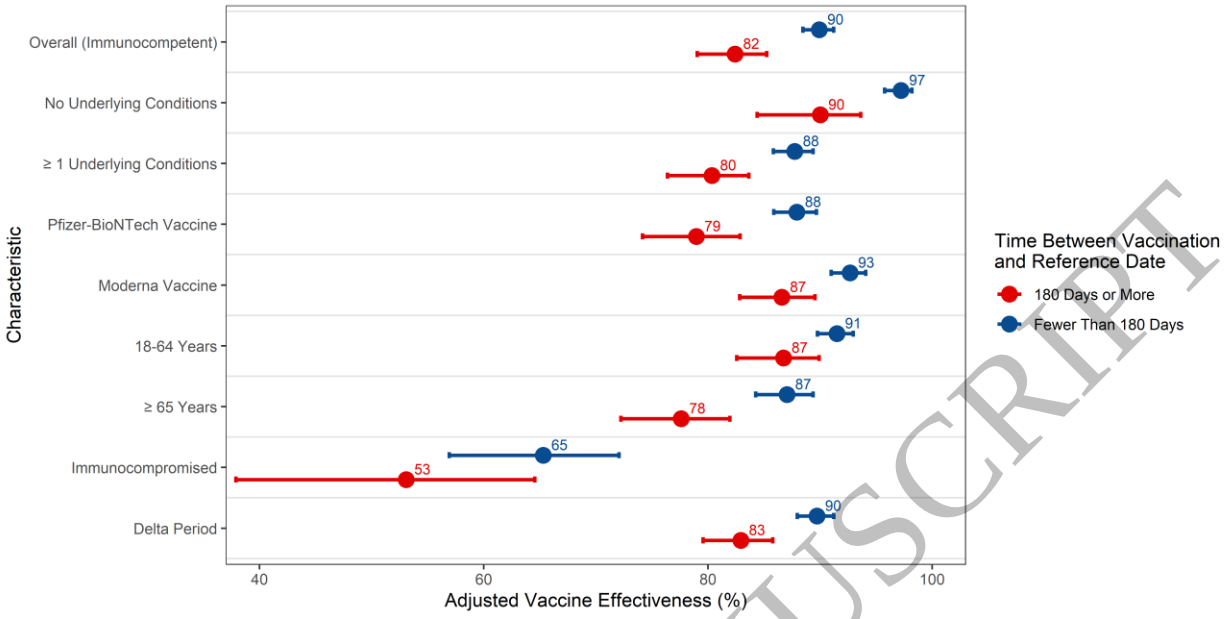

Figure 1
165x83 mm (.37 x DPI)

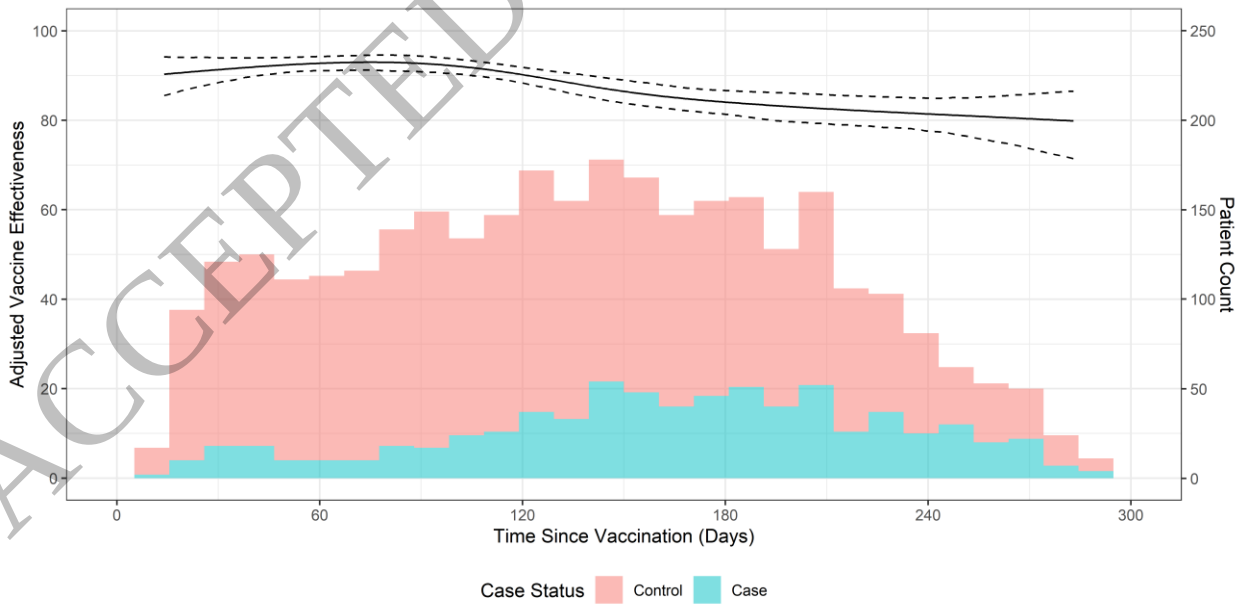

Figure 2
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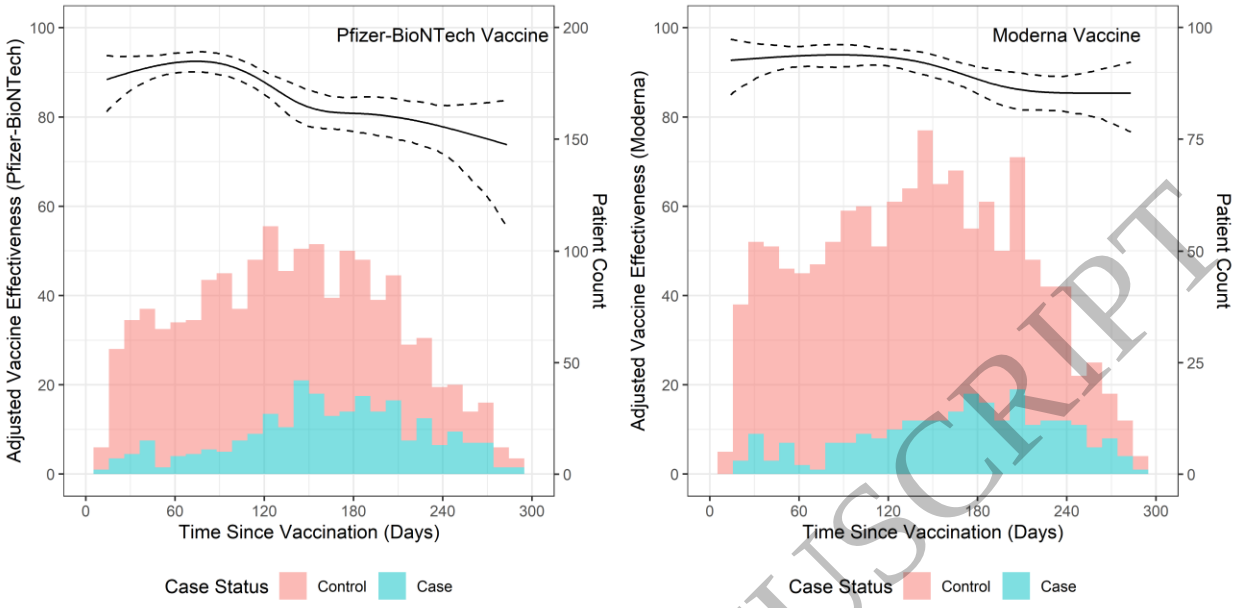

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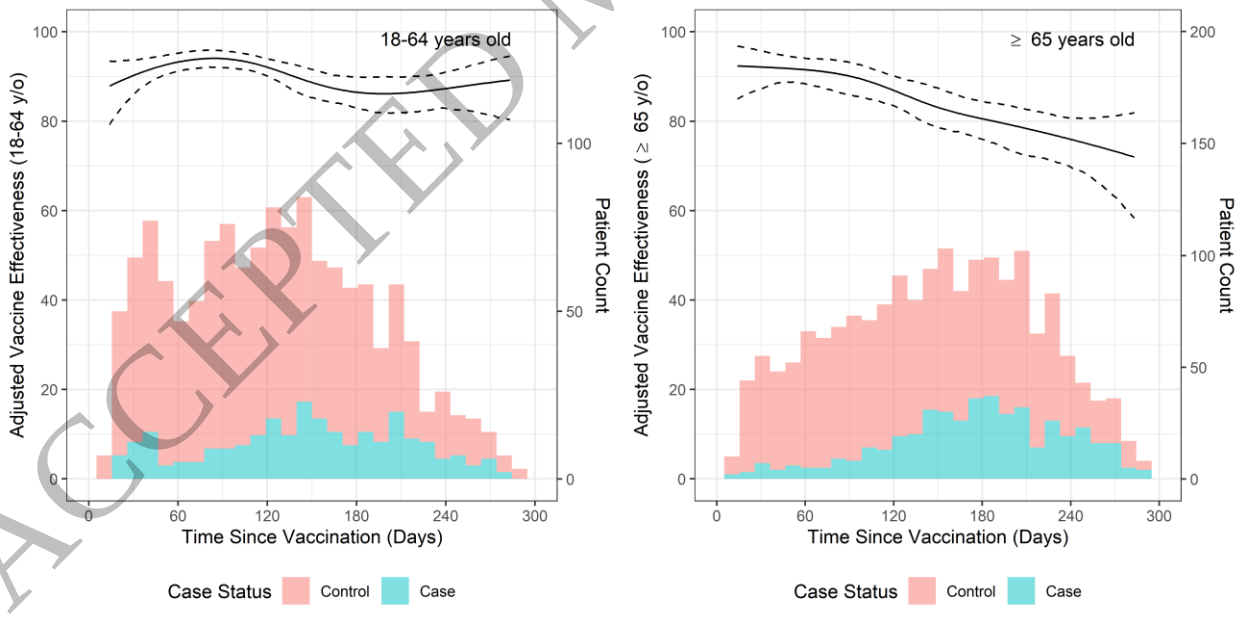

Figure 4
165x83 mm (.37 x DPI)