Take Your Best Shot: Which SARS-CoV-2 Vaccine Should I Get?

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Abstract

Background. Three vaccines against SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) have now received emergency use authorization by the US Food and Drug Administration. Patients may have the opportunity to make a choice about which vaccine they prefer to receive. Vaccine hesitancy is a hurdle to the development of widespread immunity, with many patients struggling to decide whether to get vaccinated at all. **Objective.** Develop a decision model exploring the question, "Should I get vaccinated with mRNA or adenovirus vector vaccine (AVV) if either is available now?" **Design.** Markov state transition model with lifetime time horizon. **Data Sources.** MED-LINE searches, bibliographies from relevant English-language articles. **Setting.** United States, ambulatory clinical setting. **Participants.** Previously uninfected, nonimmunized adults in the United States. **Interventions.** 1) Do Not Vaccinate, 2) Vaccination with mRNA Vaccine, 3) Vaccination with Adenovirus Vector Vaccine. **Main Measures.** Quality-adjusted life years (QALYs). **Key Results.** Base case—for a healthy 65-year-old patient, both vaccines yield virtually equivalent results (difference of 0.0028 QALYs). In sensitivity analyses, receiving the AVV is preferred if the short-term morbidity associated with each vaccine dose exceeds 1.8 days. Both vaccines afford an even greater benefit compared with Do Not Vaccinate if the pandemic is in a surge phase with a rising incidence of infection or if the current 7-day incidence is greater than the base case estimate of 105 cases per 100,000. **Conclusions.** Preferred vaccination strategies change under differing assumptions, but differences in outcomes are negligible. The best advice for patients is to get vaccinated against COVID-19 disease with whatever vaccine is available first. Providing mRNA vaccine to the remaining eligible US population would result in an aggregate gain of 3.92 million QALYs.

Highlights

Question: Now that three vaccines have received emergency use authorization to prevent SARS-CoV-2, should I get vaccinated with either the mRNA (Moderna or Pfizer) or the adenovirus vector (Janssen/Johnson & Johnson) vaccine if either one is available now?
Findings: In our base case, for a healthy 65-year-old patient, an mRNA vaccine is very slightly preferred over the adenovirus vector vaccine by 0.0028 QALYs, or slightly more than 1 day. However, both vaccines afford a substantial benefit compared with not getting vaccinated.
Meaning: In conclusion, although different vaccine strategies are preferred under different modeling assumptions, in the final analysis the differences in outcomes are extremely small. Our best advice is to simply get vaccinated with whatever is available the soonest!

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Introduction

Three vaccines against SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2), the causative agent of coronavirus disease 2019 (COVID-19) have received emergency use authorization from the US Food and Drug Administration (FDA). In contrast to the two mRNA vaccines authorized earlier (mRNA-1273 SARS-CoV-2 Vaccine [Moderna] and BNT162b2 mRNA Covid-19 Vaccine [Pfizer BioNTech]), the Ad26.COV2.S [Janssen/Johnson and Johnson] vaccine is based on an adenovirus vector, and does not have the ultracold storage requirements of the earlier vaccines. Thus, this vaccine may be easier to maintain and distribute in rural areas, or other remote sites that do not have access to ultracold refrigerators. While the adenovirus vector vaccine (AVV) only requires a single dose, it has a slightly lower efficacy against COVID-19 than the mRNA vaccines. Thus, there are tradeoffs between the AVV and mRNA vaccines. Depending upon availability, vaccination sites may have both an mRNA vaccine and the AVV, allowing patients to have a choice. Sites may also have varying availability at different times, and patients may not have a choice if they wish to get vaccinated at that time and place. Finally, vaccine hesitancy is becoming an increasing hurdle to the development of widespread community immunity, with many patients struggling to decide whether to get vaccinated at all. Our goal was to develop a decision analytic model to explore this decision.

Methods

Description of Decision Analytic Model

We used a computer program (Decision Maker) to develop a 7-state Markov transition model, using a lifelong time horizon. Our outcome metric was quality-

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adjusted life expectancy. Thus, we accounted for both survival and the impact of hospitalization, COVID-19 disease, and long-term post-infection complications on quality-of-life. We considered three strategies that an individual patient and their clinician might consider: 1) Do Not Vaccinate, 2) Vaccinate with an mRNA Vaccine, and 3) Vaccinate with the Adenovector Virus Vaccine (AVV; see Supplemental Figures S1 and S2). We also included an analysis in which we explored the scenario in which a patient who preferred getting a mRNA vaccine might have to wait if their vaccination site only had the AVV available at the time they wished to get vaccinated (i.e., vaccinate with AVV now v. wait some number of weeks to get a mRNA vaccine). We used a cycle length of 2 weeks and a lifelong time horizon for our simulation.

We performed our base case analysis for an intermediate risk, healthy 65-year-old patient, based on the median age of hospitalized patients in the Premier data base analysis.[1] We performed sensitivity analyses on key variables to examine the impact of both uncertainty in parameter estimates and clinical variability across patient characteristics. We also performed scenario analyses for patients at both low and high risk of severe illness and mortality. Finally, we also conducted an analysis examining the situation in which the Janssen vaccine is available immediately, but that a patient would need to wait some amount of time if they wanted to get an mRNA vaccine instead.

The model assumes a declining probability of COVID-19 disease that can be dynamically updated based on the current case rate in the user's county or region. For our base case, we used 7-day incidence data (April 7–13, 2021) for Hamilton County in southwest Ohio (105 cases per 100,000), which is the catchment area for the University of Cincinnati Medical Center and assumed a decline of 50 cases per 100,000 over the next year. Our analysis does not explicitly link an increasing pool of vaccinated individuals in the population to the decrease in COVID-19 incidence. We also assumed that the pandemic ends 2 years after the simulation begins, in effect bringing the 7-day incidence to zero at that time. In our base case, we explore the decision for a healthy 65-year-old, with no significant medical comorbidities.

In both vaccination strategies, the patient immediately receives a first vaccination and enters the Markov simulation in the health state—Well Without COVID-19 Post Vaccine. Studies investigating the impact of influenza infections on quality of life report decrements of between 0.32 and 0.42 (scale of 0 to 1) during each day of illness.[2,3] Since side effects experienced from the vaccines are similar to influenza symptoms (e.g., low-grade fever, myalgias, headache), we modeled the dysutility associated with

the typical transient side effects of both vaccine types by decrementing quality of life by 0.42 for a single day (i.e., 0.42 quality-adjusted days of life, or 0.00115 quality-adjusted life years) for each vaccine dose received. This is equivalent to saying that the quality of life during the roughly 24-hour period during which patients experience these side effects following each vaccine dose is 0.58.

Immunity to COVID-19 develops over time after the initial and in the case of the mRNA vaccines, the second vaccine dose. We used data from the three phase III vaccine trials to capture this increasing vaccine efficacy over time (see Table 1). In the case of the mRNA vaccine, we averaged data from both the BNT162b2 and mRNA-1273 studies to describe the increasing vaccine efficacy over time during the first month.[4,5] For the mRNA vaccine strategy, patients are scheduled to receive two doses. Patients develop increasing immunity (i.e., increasing vaccine efficacy) over time following the first and second doses. Patients who follow-up for a second dose develop full protection 2 weeks following the second dose, using published efficacy data for the mRNA vaccines. Patients who receive only a single dose of the mRNA vaccine develop partial immunity, using efficacy data from the BNT162b2 study.[5] In the base case, we assumed that 80% of patients in this strategy would follow-up for their second dose. In both strategies we assume that vaccine efficacy persists for the entire 2-year period before the pandemic ended. In all three vaccine trials, efficacy is reported for both any symptomatic COVID-19 illness and severe COVID-19 illness. In our decision model, we capture the efficacy for preventing severe illness by using different probabilities of developing severe disease for each vaccine strategy.

During each cycle of the Markov simulation, patients face a risk of COVID-19 disease modulated by vaccine efficacy. These patients may develop severe illness from which they may die. A proportion of COVID-19 disease survivors with severe illness develop long-term complications that affect quality-of-life. Patients with COVID-19 disease resulting in either mild or severe illness have a short-term utility loss, capturing the negative impact of COVID-19 disease on quality of life. In each cycle, patients also face an ever-increasing risk of death from nonexplicitly modeled causes, based on annual mortality rates as a function of age reported in life tables from the Centers for Disease Control and Prevention (CDC).[6]

Review of Data

Data used in the decision analysis are presented in Table 1. We used 7-day incidence data from the CDC[7] to calculate the probability of COVID-19 disease, specifically using data from our own geographical area of Hamilton County (contains the city of Cincinnati) in the state of Ohio.

Vaccine Efficacy. It is reported at 94% to 95% for the mRNA vaccines (Moderna mRNA-1273 and Pfizer BNT162b2) in preventing symptomatic COVID-19 disease, and 72% (95% confidence interval [CI], 58.2% to 81.7%) for the Janssen AVV (Ad26.COV2.S) in the United States.[4,5,8,9] In addition, all three trials have reported on interval efficacy data in the first few weeks following vaccination. Efficacy for the Moderna vaccine for the first 14 days, the second 14 days, and >14 days after the second dose are 54.4%, 94.2%, and 94.1% (95% CI, 89.3% to 96.8%), respectively.[4] Interval efficacy data for the Pfizer vaccine are 52.4% for the first 21 days between dose 1 and dose 2, 90.5% for the first 7 days after the second dose, and 94.8% (95% CI, 89.8% to 97.6%) for >7 days after the second dose.[10] In addition, they report an efficacy of 82% for those who have only received a single dose. Finally, the Janssen AVV reports an efficacy of zero for the first 14 days following vaccination, and 77.4% for the second 14 days after vaccination. The overall reported efficacy of 72% is for cases developing more than 28 days after vaccination.

Reported efficacy against severe COVID-19 disease is 100%, 88.9%, and 85.9%, respectively for the Moderna, Pfizer, and Janssen vaccines. As noted above, we capture this by using different probabilities of developing severe illness among vaccinated patients who develop symptomatic COVID-19. Summing data from both the Moderna and Pfizer studies, 1 out of 19 (0.053) vaccinated patients with COVID-19 developed severe disease.[4,5] In the Janssen trial, 4 out of 55 (0.073) patients with symptomatic COVID-19 developed severe disease.[10]

The situation regarding vaccines for SARS-CoV-2 is highly dynamic. On April 13, the CDC and the FDA recommended a pause in the use of the Janssen AVV vaccine in the United States "out of an abundance of caution." This followed reports of a small number of individuals who had developed cerebral venous sinus thrombosis (CVST) with thrombocytopenia after receiving the Janssen AVV vaccine. The CDC and FDA are reviewing 6 cases of CVST (after 6.85 million vaccine doses administered) in women between the ages of 18 and 48 years of age. All cases occurred within 6 to 13 days from the time of vaccine administration. One patient died.[11] Vaccine administration has resumed in Europe, and was only recently resumed (April 23, 2021) in the United States. We therefore assume an upfront mortality risk for the Janssen AVV vaccine of one in one

Table 1 Data Required in the Analysis: Probabilities, Rates, and Quality of Life

Variable	Base Case Value	95% CI or Clinically Plausible Range	Distribution Type
Average 7-day incidence of COVID-19 disease—general population (cases per 100,000)[a]	105[7]		
Annual rate of change in average 7-day incidence of COVID-19 disease (cases per 100,000 per year)	−50		
Age, base case patient, years	65		
Probability of getting second dose of mRNA vaccine	0.80	0.75–1.0	Logit
Vaccine efficacy and safety			
mRNA vaccines[4,5,8]			
First 14 days	0.532	0.30–0.68	Logit
Second 14 days	0.82	0.76–0.87	Logit
Thereafter	0.945	0.89–0.97	Logit
Single dose	0.82	0.76–0.87	Logit
Probability of severe disease	0.053	0.00–0.15	Beta
Adenovirus vector vaccine in US population[9,10]			
First 14 days	0.00		
Second 14 days	0.776	0.63–0.86	Logit
Thereafter	0.72	0.58–0.82	Logit
Probability of severe disease	0.073	0.006–0.14	Beta
Vaccine-related death	1×10^{-6}	$0.00\text{-}3 \times 10^{-6}$	Beta
Outcomes of COVID-19 disease, probabilities			
Probability of severe disease (unvaccinated)	0.102[4,5,10]	0.08–0.13	Beta
Average mortality of hospitalized patients	0.203[1,14]	0.199–0.207	Beta
Long-term complications of COVID-19 disease	0.10[16,17,19]	0.10–0.35	Logit
Quality of life			
Short-term disutility, QALYs			
Morbidity associated with each vaccine dose	0.00115[b]		
Mild COVID-19 disease	0.019[c]		
Severe COVID-19 disease	0.0769[d]		
Long-term, quality of life adjustment factor			
Long-term complications of COVID-19 ("long-haul syndrome)	0.9		

mRNA, messenger RNA; QALYs, quality-adjusted life years.
[a]Based upon average 7-day incidence in the general population of Hamilton County, OH, on April 13, 2021.
[b]Assumes 0.42 decrement in quality of life for a single day, thus 0.00115 QALYs are subtracted for each dose of vaccine received.
[c]Assumes zero quality of life for 1 week for mild COVID-19 illness, thus 0.019 QALYs are subtracted.
[d]Assumes zero quality of life for 28 days for severe COVID-19 illness, thus 0.0769 QALYs are subtracted.

million, an overly pessimistic assumption, allowing for possible upwards revision of the one death reported so far, as more data are being collected and reviewed.

Course of Disease. As of April 13, 2021, the 7-day incidence of COVID-19 disease in Hamilton County, OH, was 105 per 100,000 in the general population.[7] Roughly 10% of otherwise healthy patients with symptomatic COVID-19 disease develop symptoms of severe illness.[4,5,10,12] This also is consistent with aggregated data from the placebo arms of the three vaccine trials, in which a total of 57 patients developed severe COVID-19 illness out of the 561 patients who received the placebo vaccine and developed symptomatic COVID-19.

Studies have also identified risk factors that increase the likelihood of severe illness among those with COVID-19 disease. The strongest evidence has been found for older age, cancer, chronic kidney disease, chronic obstructive pulmonary disease, heart conditions (heart failure, coronary artery disease), obesity, sickle cell disease, pregnancy, solid organ transplantation, type 2 diabetes mellitus, and smoking.[13] In one of the largest studies that included 35,302 hospitalized patients, in-hospital mortality associated with COVID-19 disease is 20.3%.[1,14] Median age for this population was 65. Of note, older age was the risk factor most strongly associated with a higher mortality rate. In a multivariable logistic regression analysis, the adjusted odds ratio of death compared with a reference group aged 18 to 34

years increased with each 15-year increment in age (35–49 [2.12], 50–64 [4.38], 65–79 [8.58], ≥80 [16.20]).[1] A variety of baseline comorbidities, such as diabetes mellitus, hypertension, dementia, and chronic obstructive pulmonary disease, also contributed to increased mortality risk. Similar findings were reported in a recent systematic review and meta-analysis.[15] A more insidious outcome of COVID-19 disease are the long-term complications, the so-called long haul syndrome, faced by about 10% of patients surviving severe illness, although data continue to accumulate suggesting the proportion may be as high as 35%.[16-19] This syndrome is characterized by a wide variety of symptoms including cognitive issues including memory or attention problems (i.e., "brain fog"), tachycardia, dyspnea, nausea, diarrhea, and intermittent fevers among others.[18]

Results

Base Case Analysis

In the base case, results (quality-adjusted life expectancy) were very close for the two vaccine strategies, but they both were better than Do Not Vaccinate. Vaccinate with an mRNA Vaccine yielded 19.5086 QALYs; Vaccinate with the Janssen Vaccine yielded 19.5058 QALYs; while Do Not Vaccinate yielded 19.4883 QALYs. This results in a difference of only 0.0028 QALYs, or a little more than 1 day, between the two vaccines, but a difference of 0.0203 and 0.0175 between the two respective vaccine strategies and Do Not Vaccinate.

Sensitivity Analyses

We performed both deterministic and probabilistic sensitivity analyses (PSA) to examine the impact of uncertainty in parameter estimates. Deterministic sensitivity analyses were performed by systematically varying one or more parameter values over clinically relevant ranges.

Short-Term Morbidity Due to Common Vaccine Side Effects. Figure 1 examines the impact of common vaccine side effects, including myalgias, low-grade fever, and headache that typically last no more than 24 hours. In the base case, we deduct 0.42 days of quality-adjusted life expectancy for each vaccine dose. Thus, patients receiving the AVV lose 0.42 days of quality-adjusted life expectancy and those receiving an mRNA vaccine lose 0.84 days. The mRNA vaccine is preferred in the base case. However, if the dysutility associated with each vaccine dose is greater than ~1.8 days, the AVV is preferred.
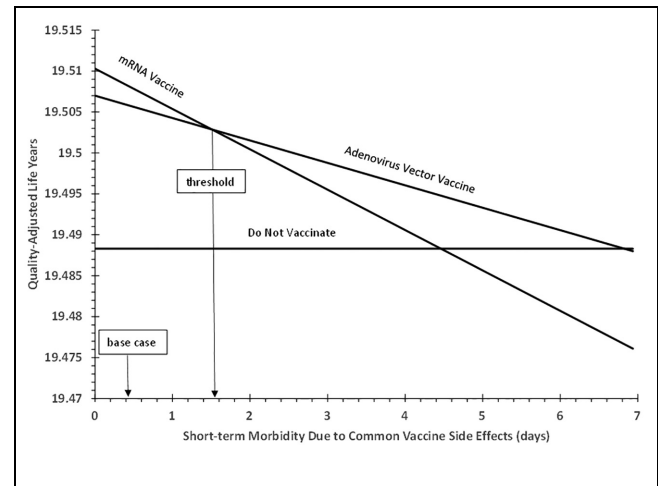

Figure 1 One-way sensitivity analysis of short-term morbidity due to common vaccine side effects. The morbidity associated with each vaccine dose is shown on the *x*-axis. In the base case, we deduct 0.42 quality-adjusted days of life for each vaccine dose received. An mRNA vaccine remains preferred unless the short-term morbidity associated with each day is greater than 1.8 days. This would be equivalent to a quality of life of zero for a time period exceeding 1.8 days following a vaccine dose.

Seven-Day Incidence of COVID-19 Disease. As shown in Figure 2, at the base case value for 7-day incidence of COVID-19 disease at the start of the simulation (105 cases per 100,000), Vaccinate with the mRNA Vaccine is best. However, if the 7-day incidence at the start of the simulation is less than 52 cases per 100,000, receiving the AVV would be best. Finally, if the 7-day incidence is <26 cases per 100,000, under the base case assumptions that the case rate is falling at 50 cases per 100,000 over the next year, then Do Not Vaccinate might be reasonable.

Figure 3 depicts a two-way sensitivity analysis examining 7-day incidence of COVID-19 and short-term morbidity due to common vaccine side effects. In the region to the upper left, where COVID-19 incidence is low and short-term morbidity due to vaccine side effects is high, Do Not Vaccinate is best. In the region at the lower right, where Covid-19 incidence is high and short-term morbidity due to vaccine side effects is low, vaccinate with a mRNA vaccine is best. In the middle region, with intermediate values for Covid-19 incidence and vaccine side effects, vaccinate with the AVV is best.

Trajectory of COVID-19 Pandemic. We also examined the trajectory of the COVID-19 pandemic. In our base case we assumed a declining 7-day incidence, consistent
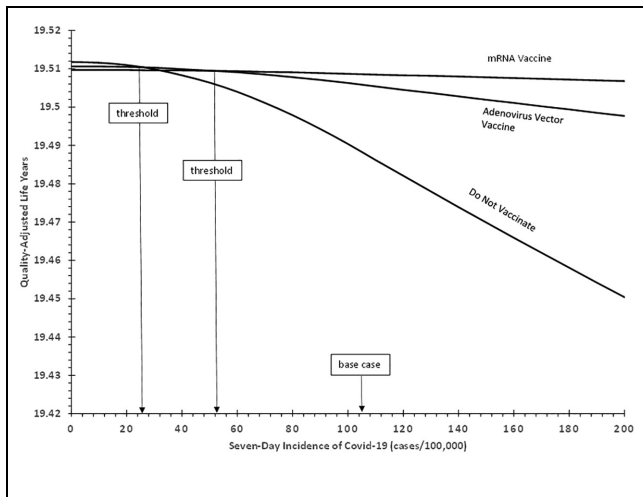
Figure 2 One-way sensitivity analysis of 7-day incidence of COVID-19 illness. The average 7-day incidence of COVID-19 disease (cases per 100,000) at the start of the simulation is shown on the *x*-axis. At the base case value of 105, the mRNA vaccine is best. Below a threshold of 52 cases per 100,000 as the average 7-day incidence, vaccination with AVV would become preferred, although by a small margin, and if the 7-day incidence is <26 cases per 100,000 then Do Not Vaccinate might be reasonable. If the average 7-day incidence were to increase, as during a COVID-19 surge, the gain afforded by either vaccine increases substantially compared with Do Not Vaccinate.

with a resolving pandemic. We performed sensitivity analyses examining the possibility that at any time the incidence may be rising or falling. As shown in Figure 4, in the base case when the 7-day incidence is declining at 50 cases per 100,000 per year, Vaccination with an mRNA Vaccine is best. This continues to be the case if the pandemic recurs with an increasing weekly case count. However, if the case rate were declining at a rate greater than 190 per 100,000 per year, receiving the AVV would be preferred by a very slight margin.

Supplemental Figure S3 shows the 7-day incidence in all three strategies under the base case assumption that the 7-day incidence over time is declining at 50 cases per 100,000 per year. This is likely a more accurate representation of the pandemic, assuming there is not a recurrent surge, perhaps due to more contagious viral variants. Of note, this analysis does not assume the overall population incidence is decreasing as a larger proportion of the population gets vaccinated.

Proportion of mRNA Vaccine Recipients Receiving Second Dose. Another important variable is the proportion
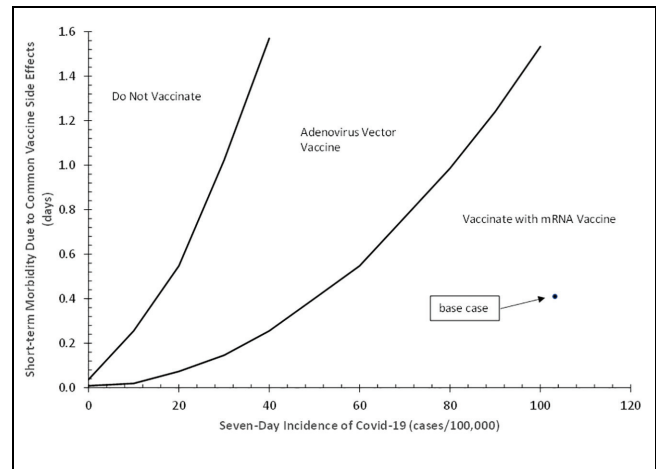

Figure 3 Two-way sensitivity of 7-day incidence of COVID-19 cases and short-term morbidity due to common vaccine side effects. The 7-day incidence of COVID-19 cases (cases/100,000) is shown on the *x*-axis, while the short-term morbidity due to common vaccine side effects (days) is on the *y*-axis. The two curves across the graph show the thresholds between the two vaccine strategies and Do Not Vaccinate. Along the threshold line, the difference in expected utility between strategies on either side of threshold line is zero. In the region emanating from the upper left, where Covid-19 incidence is low and short-term morbidity due to vaccine side effects is high, Do Not Vaccinate is best. In the region emanating from the lower right, where COVID-19 incidence is high and short-term morbidity due to vaccine side effects is low, Vaccinate with an mRNA Vaccine is best. In the middle region, with intermediate values for COVID-19 incidence and vaccine side effects, Vaccinate with the AVV is best. The base case falls in the region to the lower right, in which Vaccinate with an mRNA Vaccine is best.

of patients who receive the second dose of the mRNA vaccine. In the base case we assumed 80%. Our results are not sensitive to this variable, as the mRNA vaccine is still preferred even if no one gets a second dose. This is because the efficacy of even a single dose of the mRNA vaccine is 82%, compared with the efficacy of the AVV, which is 72%.

Quality of Life among Patients with Long-Term COVID-19 Complications ("Long-Haul Syndrome"). Absent any published quantitative assessment of the quality-of-life among patients with the so-called long-haul syndrome of post-COVID-19 complications, we used a base case value of 0.9 based on the expert opinion of our infectious disease collaborators. Model results were not sensitive to changes in this parameter value across the range of 0.5 to 1.0.
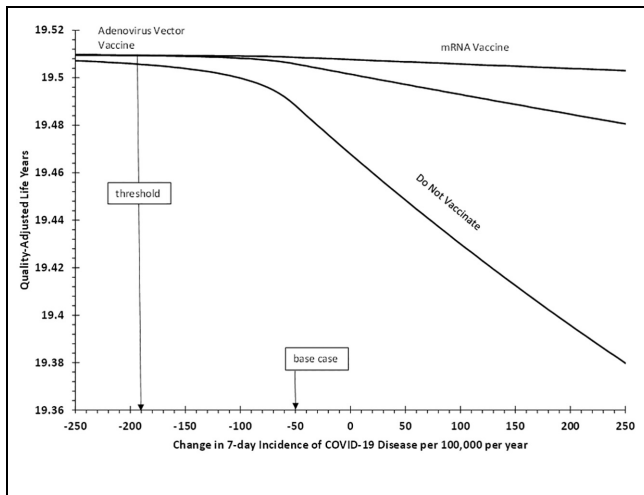
Figure 4 One-way sensitivity analysis on the annual change in average 7-day incidence of COVID-19 disease per 100,000 patients. In the base case we assumed that the pandemic was in a declining phase, during which the average 7-day incidence was declining at a rate of 50 cases per 100,000 patients each year. At the base case value, receiving an mRNA vaccine is best. If the rate of decline in cases is larger (decline greater than ~190 cases per 100,000 per year), AVV becomes preferred, but only by a very small margin. As in Figure 2, if the change in 7-day incidence of COVID-19 disease actually increases, as might occur during a surge, both vaccines afford an increasing benefit compared with Do Not Vaccinate.

Impact of SARS-CoV-2 Variants. We also explored the potential impact of an increasing prevalence of SARS-CoV-2 variants, such as the B.1.351 variant (South African variant). The AVV reported an efficacy of 58% in South Africa where the new SARS-CoV-2 variant is circulating.[9] We do not have data on the efficacy of the mRNA vaccines for this variant; if we assume efficacy decreases from 94.5% to 85%, while using the 58% efficacy reported above for the AVV, the mRNA vaccine is still preferred, although by a smaller margin—19.5075 versus 19.5034. Both vaccines are still preferred over Do Not Vaccinate.

mRNA Vaccine Delay. We also explored a scenario in which a patient who preferred getting a mRNA vaccine might have to wait if their vaccination site only had the AVV available at the time they wished to get vaccinated. As shown in Figure 5, the mRNA vaccine remains slightly preferred unless the delay to receive it extended beyond 12 weeks.
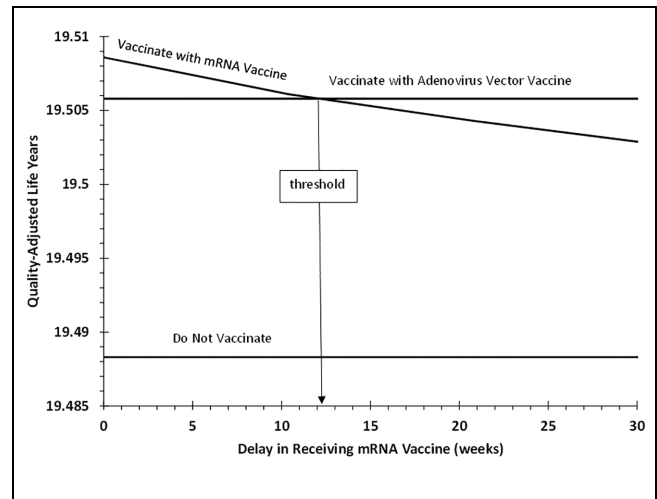

Figure 5 One-way sensitivity analysis of delay to receive mRNA vaccine. The delay to receive the first dose of an mRNA vaccine is shown on the *x*-axis in weeks. QALYs for each of the two strategies is shown on the *y*-axis. As long as the delay to receive an mRNA vaccine is less than 12 weeks, waiting for a mRNA vaccine is preferred, again by a very small margin.

Clinical Scenarios

In the base case we analyzed results for an intermediate risk individual. Advancing age along with certain medical comorbidities have been shown to increase both the risk of severe illness and the risk of death from COVID-19 disease.[1,12,14] We next explore clinical scenarios of a high-risk patient and a low-risk patient (Figure 6).

High-Risk Patient. In this scenario, we analyze results for a prototypical high-risk patient. We selected the following characteristics for this patient, based on adjusted odds of mortality described in a multivariable logistic regression model developed on 35,302 patients hospitalized for COVID-19 disease in the Premier data base.[1] Age ≥80 (16.2, 95% CI, 11.58 to 22.67), diabetes (1.20, 95% CI, 1.12 to 1.28), cerebrovascular disease (1.39, 95% CI, 1.25 to 1.56), congestive heart failure (1.37, 95% CI, 1.26 to 1.49), and chronic pulmonary disease (1.16, 95% CI, 1.08 to 1.1.26).

The reference case was a patient between the ages of 18 and 34 with no medical comorbidities. If we assume that all deaths in this age group were among patients with severe disease (49/2272), mortality for this group was 0.022. The odds of death for a patient with the risk
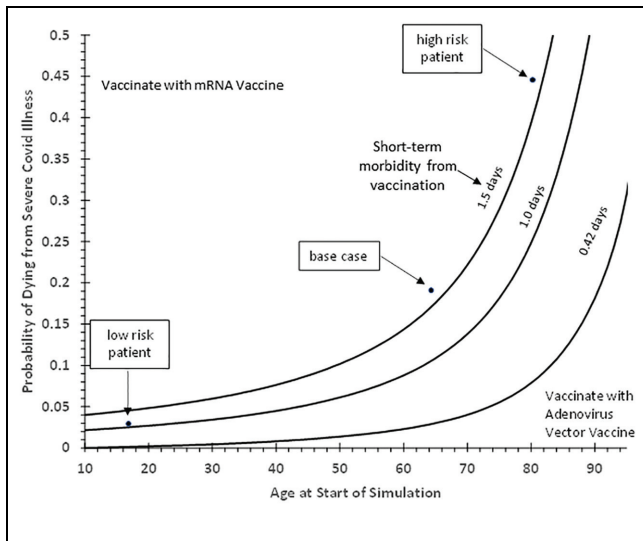
Figure 6 Three-way sensitivity analysis of age, probability of dying from severe COVID-19 disease, and short-term morbidity from vaccination. The age of patients at the start of the Markov simulation is shown on the *x*-axis, while the probability of dying from severe COVID-19 illness is shown on the *y*-axis. The three curves depict the thresholds between the two vaccine strategies for different values of short-term morbidity from vaccination, the base case value of 0.42 days (bottom right), 1 day (middle curve), and 2 days (curve at the upper left). Along each threshold line, the difference in expected utility between both strategies is zero. Above the lines, in the region emanating from the upper left, in which patients are younger and the probability of death from severe COVID-19 illness is higher, Vaccinate with an mRNA Vaccine is best. In the region emanating from the lower right, in which patients are older the risk of dying from severe COVID-19 illness is lower, Vaccinate with the AVV is best. The region to the bottom right, in which AVV is best gets larger as the short-term morbidity associated with each vaccine dose increases. Three clinical scenarios are highlighted, including the base case (otherwise healthy 65-year-old), a high-risk patient (age ≥80 years with multiple comorbidities), and a low-risk patient. All fall within the region in which an mRNA vaccine is preferred at the base case value for vaccine morbidity. Note, a >80-year-old patient with no other comorbidities has a calculated mortality risk of 26.3% (not shown in figure).

factor profile above is 0.876, resulting in a 46.7% probability of death.* Since this is an overall mortality and not specific for patients with severe disease, we only used

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* Odds of death for patient ≥80 years of age, with comorbidities of diabetes, cerebral vascular disease, congestive heart failure, and chronic obstructive pulmonary disease = odds of death in 18–34 ($0.0214 \times 16.2 \times 1.2 \times 1.39 \times 1.37 \times 1.16$) = 0.918. Probability of death = (odds/odds + 1) = (0.918/1.918) = 0.479.

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this mortality risk and did not vary the probability of severe disease in this scenario analysis. For an 80-year-old with this risk factor profile Vaccinate with an mRNA Vaccine remains preferred over the AVV, although by a small margin, 9.3956 versus 9.3927 QALYs. However, the gain from either vaccine compared to Do Not Vaccinate (9.3744) is 0.0212 and 0.0183 QALYs, respectively.

Low-Risk Patient. For an 18-year-old with no comorbidities, an mRNA vaccine is the preferred strategy, although by a very small margin, 61.7615 versus 61.7604, respectively. Do Not Vaccinate yields 61.7520 QALYs. Figure 6 shows a three-way sensitivity analysis exploring age at the start of the simulation and the probability of dying from severe COVID-19 illness. The two prior clinical examples are illustrated along with the base case.

Probabilistic Sensitivity Analysis. We conducted a PSA by performing 10,000 second-order Monte Carlo simulations.[20] Distributions for parameter values were developed (see Table 1) using beta and logit distributions for probabilities. The mRNA vaccination strategy was best in 66.52% of simulations, while vaccination with the AVV was best in the remaining 33.48% of simulations. Do Not Vaccinate was never preferred. Mean expected utilities and standard deviations for the three strategies were 19.5054 (0.0013), 19.5042 (0.0025), and 19.4884 (0.0028), respectively. As shown in Figure S4, Panel 1, the mean gain in expected utility between the mRNA vaccine and the AVV was 0.0012 (0.0028) QALYs. Panels 2 and 3 show the mean gain between the two vaccines and Do Not Vaccinate, 0.0170 (SD 0.0031) and 0.0158 (SD 0.0037) QALYs, respectively.

Discussion

Patients and their clinicians face a potentially confusing choice regarding whether to accept vaccination with one of the mRNA vaccines, which require two doses, or a single dose of the AVV. Data suggest that the mRNA vaccines have a somewhat higher efficacy (95% v. 72%) than the AVV. In addition, one death due to CVST has been described among the more than 6.85 million patients receiving the AVV. Side effects during the 24 hours following all three vaccines are common, including myalgias, low-grade fever, and headache. Thus, some patients may prefer the convenience of a vaccine that only requires a single dose, and thus a single day of side

effects, without the need to schedule a second visit to a vaccination center.

In our base case analysis, for an otherwise healthy 65-year-old patient getting vaccinated with a mRNA vaccine results in a small gain in quality-adjusted life expectancy of 0.0016 QALYs compared with the AVV, or ~6/10's of a day. However, receiving either vaccine resulted in a gain of 0.0203 and 0.0175 QALYs compared with Do Not Vaccinate. With regard to impact on the eligible but currently unvaccinated population in the United States, the most recent population estimates from July 2019, estimate there are 255,200,373 people 18 years of age and older, and another 8,711,434 between the ages of 16 and 17 years.[21] Prior to May 10, 2021, individuals 16 years of age and older were eligible to receive a COVID-19 vaccination. As of April 20, 2021, 87.6 million Americans have been fully vaccinated, leaving 176.3 million Americans 16 years of age and older not fully vaccinated. On May 10, 2021, the FDA authorized the Pfizer-BioNTech COVID-19 vaccine for emergency use in adolescents 12 through 15 years of age, adding another 16,633,058 unvaccinated but eligible patients, for a total of 192,944,865.[21,22] Extending the results of our analysis to the population still eligible to receive a vaccine, providing a mRNA vaccine to the remaining eligible US population would result in an aggregate gain of 3.92 million QALYs, while vaccinating the remaining eligible US population with the AVV vaccine would result in an aggregate gain of 3.38 million QALYs.

Key assumptions in our analysis were that the pandemic was in a declining phase, that vaccine side effects were sufficiently common that we deducted a small toll for the transient decreased quality of life during the 24 hours following each vaccine dose, and that only 80% of patients receiving an mRNA vaccine would get their second dose. Sensitivity analyses examining these assumptions showed that the benefit of vaccination with either product would yield an even larger gain if we had another surge in COVID-19 illness, as has occurred in other countries such as India. As an example, if the change in 7-day incidence were to shift from the base case assumption of a decline of 50 cases/100,000 per year to an increase of 100/100,000 per year, an mRNA vaccine would yield a benefit of 0.076 QALYs compared with Do Not Vaccinate. With regard to the transient morbidity associated with each vaccine dose, we found that a modest increase from the base case assumption of a 0.42 days of symptoms (decrement of 0.42 for that one day) to 1.5 days would make vaccination with the AVV preferable for a younger patient at low risk of dying from severe COVID-19 illness. Our results were insensitive to assumptions regarding the proportion of patients receiving a second dose of an mRNA vaccine, as the efficacy of even a single dose was superior to the AVV. We also performed a scenario analysis in which a patient who preferred getting an mRNA vaccine might have to wait if their vaccination site only had the AVV available at the time they wished to get vaccinated. We found that the delay to wait for an mRNA vaccine would have to exceed 12 days before vaccination with AVV would become preferred. We also explored clinical scenarios for patients at low and high risk of inpatient mortality from COVID-19 disease.

Our analysis has a number of limitations. First, efficacies reported for the three vaccines were obtained at different time points, in different countries, and using slightly different end points. There are no head-to-head comparisons available. While this is important when trying to compare vaccines, we are not likely to have a simultaneous study of multiple vaccines in the same population. Thus, we used the best data currently available. In our base case analysis, we did not make any assumptions about an increasing prevalence of SARS-CoV-2 variants, such as the South African strain, for which the AVV has a decreased efficacy. Using the reported efficacy of 58% for the AVV in South Africa, we did, however, explore this in a sensitivity analysis. While an mRNA vaccine is preferable in this sensitivity analysis, we did not have firm data upon which to base a presumably decreased efficacy for the mRNA vaccines. Based on expert opinion, we used an efficacy of 85% (v. the reported efficacy of 95%) in this scenario. However, vaccination with the AVV would become preferable if the efficacy of the mRNA vaccines dropped below 66% in the presence of highly prevalent vaccine resistant strains. That being said, while manufacturers may be working on boosters to increase coverage for variants, we did not model possible improvements in vaccine efficacy in this sensitivity analysis. Finally, our analysis did not directly tie decreased population incidence of COVID-19 to the results of the vaccination strategies being explored in the model. We did assume a declining 7-day incidence of infection. No doubt this is, in part, a result of vaccination campaigns across the country, but changes in the effectiveness of the strategies explored in our model do not impact the decline in 7-day incidence. Thus, at a population level our model likely underestimates the benefit of vaccination.

In conclusion, despite a concerning reports of a mortality risk associated with the adenovirus vector vaccine, at least in younger women, given the morbidity and

mortality associated with SARS-CoV-2 infection, getting vaccinated with either a mRNA or adenovirus vector vaccine is still better than not getting vaccinated, even in lower risk populations. Many, if not most patients, do not have the opportunity to make a choice about which vaccine to receive. They show up at a vaccination site and get whatever is available at that time. However, as evidence continues to solidify, policy decisions may be guided by nuances maximizing use of different vaccines in different populations. To date, all cases of CVST have occurred in women under the age of 48. If choices can be made, it might be reasonable to use one of the mRNA vaccines in this population. Other situations make use of the adenovirus vector vaccine more appealing, as in populations for whom assuring a second dose can be given is a greater challenge, or vaccination sites in more isolated areas where strict refrigeration of vaccine is not feasible. No doubt policy will need to remain nimble as we continue to learn more about these vaccines in wider public use.

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Supplemental Material

Supplementary material for this article is available on the *Medical Decision Making Policy & Practice* website at https://journals.sagepub.com/home/mpp.

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