AEI ECONOMIC PERSPECTIVES

Real-World Assessments of COVID-19 Vaccine Efficacy

By James C. Capretta, Scott Ganz, and Kieran Allsop

October 2021

Over the past year, the global vaccination campaign to end the COVID-19 pandemic has progressed from tests of vaccine efficacy to over six billion (and counting) administered doses. Highly structured clinical trials facilitated strong statistical examinations of the vaccines because randomization accounts for unobserved confounders that could bias the analysis. Post-approval assessments have limitations because they rely on data from less structured, real-world settings. Several post-approval studies show the existing mRNA vaccines launched initially in the US effectively prevent, as predicted, the worst outcomes of COVID-19, while the vaccines many other countries use are less effective but still invaluable in fighting the pandemic. An observed erosion in vaccine efficacy this year, relative to the clinical trials of 2020, may be a function of the new variants of the virus, waning acquired immunity against infection over time, or other factors, such as the higher incidence of prior infections in the unvaccinated population and the tendency for random error (such as false-positive COVID-19 tests) to attenuate measured efficacy rates. Taken together, the studies make it plain that vaccinating the unvaccinated with any of the globally approved vaccines remains the most important step for lessening the pandemic's severity.

Governments worldwide have administered over six billion COVID-19 vaccines since late 2020 (Our World in Data 2021a), using inoculations developed by both Western companies and state-directed enterprises in other parts of the world. In clinical trials, some of the vaccines performed better than others did in preventing symptomatic infection. It remains an open question whether populations with access to the best-performing vaccines enjoy a meaningful advantage in addressing the crisis.

Policymakers must continue to monitor the performance of the vaccines to be prepared to adjust their operational plans. However, interpreting the data is more challenging when it is obtained from real-world settings than from a clinical trial because there is not a well-defined control group against which vaccination can be assessed. In clinical trials, random assignment to the treatment and non-treatment arms allows for gold-standard statistical assessments of efficacy. In the real world, however, statistical confounders risk distorting estimates of vaccine efficacy and how efficacy differs among vaccines and over time.

Recently, numerous studies have looked into the vaccines' relative performances, focusing on measuring their efficacy against the new variants of the

virus and the length of protection they provide. The source data come from the measured infection, hospitalization, and death rates in countries deploying the various vaccines. While we caution against overemphasizing the results of any single study, the weight of the evidence derived from studies relying on various statistical methods can help inform policy decisions for managing the crisis.

Post-Approval Efficacy Assessment

By late summer 2021, sufficient time had elapsed from the beginning of mass vaccination programs in the preceding winter and spring to permit estimation of the real-world efficacy rates of COVID-19 vaccines. Unlike the randomized controlled trials that were used to evaluate efficacy before vaccine approval, these studies are based on observational data collected in the field. The benefits of these studies are threefold. First, they offer updated guidance to policymakers and the public as the pandemic continues to evolve. Second, due to the massive scale of the vaccination effort, they provide new insights into the efficacy of vaccines on certain subpopulations that were too small in the original trials to provide statistically reliable results. Third, large-scale studies of vaccination programs help uncover unexpected outcomes that are too rare to be detected in the smaller experiments.

On the other hand, observational studies sacrifice the internal validity guaranteed by the structure of a randomized controlled trial. Randomization of the treatment in a clinical trial ensures consistent estimates of the vaccine efficacy rate for the population under study. In contrast, when using observational data, analysts are forced to account for nonrandom assignment to the treatment. In other words, adults who received the vaccine likely differ from those who did not in observable and, perhaps, unobservable ways. Additionally, observational studies face numerous data limitations that are not a factor in vaccine trials with voluntary participation. Whereas trial volunteers are subject to continuous surveillance to accurately assess whether and when they contract COVID-19, for example, many observational studies rely on adults getting tested once they become sick, which may not be a reliable means of ascertaining infection rates, and have imperfect data on vaccination status, which biases estimates of vaccine efficacy toward zero.

Therefore, unlike in clinical trials in which randomized treatment assignment is the agreed gold standard, drawing inferences about the real-world efficacy of COVID-19 vaccines involves integrating conclusions from a series of studies, each of which confronts these data imperfections differently, depending on the limitations of the setting and the design of the study.

Despite these hurdles, retrospective studies based on real-world data can be informative when clear patterns emerge. The good news is that several studies published in late summer and early fall 2021 tell a remarkably similar story: The novel mRNA vaccines from Pfizer-BioNTech and Moderna are proving highly effective at preventing severe cases of COVID-19 for all segments of the population

Table 1. Vaccines with the Highest Use Globally

Name	Manufacturer	Technology	US Approval*	WHO Approval
Ad26.COV2.S	Johnson & Johnson	Viral Vector	Yes	Yes
BBIP-CovV	Sinopharm	Deactivated Virus	No	Yes
BNT162b2	Pfizer-BioNTech	mRNA	Yes	Yes
ChadOx1nCoV-19	Oxford-AstraZeneca	Adenovirus Vector	No	Yes
CoronaVac	Sinovac	Deactivated Virus	No	Yes
mRNA-1273	Moderna	mRNA	Yes	Yes
Sputnik V	Gamaleya Research Institute	Adenovirus Vector	No	No

Note: * Emergency use approval. (On August 23, 2021, the Food and Drug Administration gave full approval to the Pfizer-BioNTech vaccine for persons age 16 and older.)
Source: Authors.

across many countries worldwide, and other vaccines, while less effective, are important tools in battling a global pandemic (Table 1).

The following is a brief review of the evidence on these and other vaccines at this stage of the pandemic, with a focus first on studies conducted in the United States and then on the most relevant reviews of the highest-use vaccines globally. In the process, we describe key design considerations in the studies that policymakers and the media are citing and how those considerations likely affect estimated efficacy rates.

Representative Studies in the United States

Studies based on four distinct populations of US adults were released in August and September 2021. Differences in the data collection strategies across the four populations required the authors to use different statistical methods for estimating vaccine efficacy. However, studies of all four populations show continued strong protection for the mRNA vaccines against severe COVID-19. There is also some evidence that vaccine efficacy is weaker against the delta variant and for older adults. Further, there is suggestive evidence that the Moderna vaccine provides stronger protection than the Pfizer-BioNTech vaccine does, which itself provides stronger protection than one dose of the Johnson & Johnson vaccine.

IVY Network Study. The Influenza and Other Viruses in the Acutely Ill (IVY) Network, a group created by the Centers for Disease Control and Prevention (CDC) that was originally set up to estimate how well influenza vaccines work, aggregated data from 21 hospitals across 18 states to evaluate the efficacy of COVID-19 vaccines against severe illness.

Wesley Self et al. (2021) analyze the data collected by the network using a case-control analysis in which patients who were admitted to a hospital for exhibiting COVID-19-like symptoms and tested positive for the virus are compared against those who tested negative for COVID-19. This control group included "test-negative controls"—individuals who came to the hospital with COVID-19-like symptoms but tested negative for the virus—and "syndrome-negative controls"—those who were tested at the hospital for reasons unrelated to COVID-19-like symptoms. In all, the analysis included 3,689 patients admitted to a hospital in the network who were age 18 or over and did not have immunocompromised conditions.

In a case-control study, vaccine efficacy is determined based on the relative proportions of vaccinated adults in the case and control groups. This design can be straightforwardly implemented based on observational data if there is sufficiently detailed information on the COVID-19 risk characteristics of the cases and a sufficiently large pool of potential control patients to match them with. But this design also requires valid matching between the case and control groups to accurately estimate vaccine efficacy. If unobservable characteristics differ between the two groups that are correlated with vaccination status, such as the likelihood of engaging in behaviors that increase infection risk or the probability of going to a hospital conditional on infection, the estimated efficacy rate will be biased.

The study was conducted between March and August 2021 and finds the Moderna vaccine to have a marginally higher efficacy in reducing COVID-19 hospitalizations than that produced by Pfizer-BioNTech: 93 percent (confidence interval (CI): 91–95 percent) versus 88 percent (CI: 85–91 percent).[1] Both mRNA vaccines are found to be substantially more effective in reducing hospitalization than that of Johnson & Johnson, which had estimated efficacy of 71 percent (CI: 56–81 percent). The study also finds that the efficacy rate for the Pfizer-BioNTech vaccine declines to 77 percent (CI: 67–84 percent) for adults more than 120 days post–full vaccination. The Moderna vaccine, in contrast, has nearly equal efficacy rate for less recently vaccinated adults (92 percent, CI: 87–96 percent) as it does for more recently vaccinated adults.

[1] When possible, we present both point estimates and 95 percent CIs when summarizing study results. Generally, point estimates with nonoverlapping CIs indicate statistically significant differences. However, because of the variety of the methodological approaches in the studies and the potential for multiple-hypothesis tests to be appropriate for some comparisons, we decline to comment on the presence or absence of statistical significance in any single study.

The VISION Network Study. The Vaccine Effectiveness Using Integrated Medical and Public Health Record (VISION) network consists of seven health care systems around the US that administrate 187 hospitals and 221 emergency departments and urgent care clinics (EDUC) that are collaborating with the CDC to monitor the effectiveness of COVID-19 vaccines against laboratory-confirmed infections and associated hospitalizations, intensive care unit (ICU) admissions, and EDUC encounters. The health care systems treat adults in California, Colorado, Indiana, Minnesota, New York, Oregon, Utah, Washington, and Wisconsin.

Two studies based on the VISION network data were published in early September 2021. Mark Thompson et al. (2021) examine data from January through June 2021, focusing on the real-world efficacy of vaccines for adults over age 50. Shaun Grannis et al. (2021) use data from June through August 2021 to evaluate the efficacy of vaccines against COVID-19 when the delta variant was prominent.

Both studies use a test-negative design to estimate the vaccine efficacy rate against hospital admission and EDUC visits. The test-negative design is based on the relative proportions of adults at the facilities with COVID-19-like symptoms who test positive for COVID-19 conditional on vaccination status. The benefits of this study design are twofold. First, it returns an unbiased estimate of vaccine efficacy against hospitalization and EDUC encounters if vaccinated and unvaccinated individuals are equally likely to (1) seek medical care given the same set of COVID-19-like symptoms and (2) contract non-COVID-19 diseases with COVID-19-like symptoms. It is not clear how likely it is for these assumptions to hold in this instance.

Second, because the test-negative design does not require tracking adults who are asymptomatic, it permits analyses of large, representative samples of the population of interest. Of note, because tests are administered to all patients with COVID-19-like symptoms, the study design also implicitly controls for the probability of being tested (i.e., so long as individuals with COVID-19-like symptoms go to hospitals or EDUC clinics with equal probability conditional on vaccination status), which is an important confounding variable in other study designs.

Based on data on 41,552 hospitalizations and 21,522 EDUC visits, Thompson et al. (2021) estimate that overall effectiveness of the mRNA vaccines—for adults over age 50 receiving two doses—against hospitalization is 89 percent (CI: 87–91 percent) and against EDUC visits is 91 percent (CI: 89–93 percent). Similar efficacy rates were observed for ICU admissions, patients with a chronic respiratory condition, and Black and Hispanic patients. However, for adults over age 85, the study finds lower efficacy rates: 83 percent (CI: 77–87 percent) and 84 percent (CI: 73–91 percent) for hospitalization and EDUC encounters, respectively.

This study also observes modest differentiation in efficacy across the different vaccines, finding the Moderna vaccine most effective against hospitalization (91 percent, CI: 89–93 percent) and EDUC encounters (92 percent, CI: 89–94 percent), the Pfizer-BioNTech vaccine marginally less effective against hospitalization (87 percent, CI: 85–90 percent) and EDUC encounters (89 percent, CI: 85–91 percent), and Johnson & Johnson's vaccine least effective against hospitalization (68 percent, CI: 50–79 percent) and EDUC encounters (73 percent, CI: 59–82 percent).

Grannis et al. (2021) focus on the summer, when the delta variant was predominant, and include data on hospitalizations and EDUC visits for all adults, not just those over age 50. The study estimates an overall efficacy rate of 86 percent (CI: 82–89 percent) against hospitalization and 82 percent (CI: 81–84 percent) against EDUC encounters. Thus, even during the recent delta variant–driven wave of COVID-19 infections, the study finds that vaccines provide strong protection against serious illness. Consistent with findings by Thompson et al. (2021), the study finds that vaccine efficacy is weaker for adults over age 75 than for adults younger than 75 years old—76 percent (CI: 64–84 percent) and 89 percent (CI: 85–92 percent), respectively. The study also finds a similar pattern of relative efficacy across the three vaccines. The efficacy rate for adults against hospitalization who received the Moderna vaccine (95 percent, CI: 92–97 percent) exceeds the efficacy rate for the Pfizer-BioNTech vaccine (80 percent, CI: 73–85 percent) and the Johnson & Johnson vaccine (60 percent, CI: 31–77 percent).

The HEROES-RECOVER Cohort Study. Another recent study of note is a cohort assessment of 4,136 frontline workers across six states who have been tested weekly for COVID-19 since December 2020

(Fowlkes et al. 2021). The benefits of the cohort study design are twofold. First, because all participants are tested weekly, it captures data on both symptomatic and asymptomatic adults. Second, the regular testing required to remain in the study eliminates the potential that vaccination status is correlated with the likelihood of being tested for COVID-19 or the frequency of the tests.

The major drawback is that, if the cohort does not represent the broader population both in baseline risk factors and exposure to COVID-19, then the estimated efficacy rate will depart from the rate in the broader adult population. In this case, the Healthcare, Emergency Response and Other Essential Workers Surveillance–Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (HEROES-RECOVER) study only includes health care personnel, first responders, and other essential and frontline workers.

A related concern is that, over time, the proportion of the sample that is unvaccinated may shrink to the point that it becomes impossible to make precise or unbiased inferences about the efficacy of the vaccine. During the initial phase of the US mass vaccination program, limits on the supply of vaccines excluded some frontline workers from accessing shots, which ensured a nontrivial portion of the cohort remained unvaccinated. By the conclusion of the study, however, 83 percent of study participants were vaccinated. The low number of unvaccinated participants, along with concerns that unvaccinated frontline workers may differ from vaccinated frontline workers in unobservable ways, complicates estimation of efficacy rates in the latter stages of the study window.

Even with these drawbacks, however, the results from the cohort analysis are largely consistent with the other analyses. Over the entire study period, the estimated vaccine efficacy rate against infection was 80 percent (CI: 69–88 percent). In regions where the delta variant was not predominant, however, the efficacy rate was 91 percent (CI: 81–96 percent). When the delta variant was predominant, the estimated efficacy rate declined to 66 percent (CI: 26–84 percent). Note, however, the wide confidence interval on the latter estimate.

Kaiser Permanente Southern California Study. Sara Tartof et al. (2019) analyze data from individuals who are members of Kaiser Permanente Southern California (KPSC) to estimate the efficacy of the Pfizer-BioNTech vaccine and examine whether vaccine efficacy wanes in the months following vaccine administration. The study is based on data from electronic health records for 3.4 million KPSC members age 12 years and older who had been members for more than one year. Within this subset, 33.4 percent of individuals received at least one dose of the Pfizer-BioNTech vaccine. Data on vaccination status are collected from the California Immunization Registry, a state-run database of all vaccinations administered by California providers. The study was conducted from mid-December through early August. Members who received a different COVID-19 vaccine were excluded from the analysis upon being vaccinated.

The cohort design in the study has benefits and drawbacks relative to the alternative designs. The major advantage of this study is its sheer size. By drawing on a database of millions of members, the authors can estimate efficacy rates conditional on age, time since vaccination, and COVID-19 variant with greater accuracy than other approaches. This design is also more susceptible to statistical confounders that could bias estimated efficacy rates. Of particular concern are unobserved characteristics of members that are correlated with vaccination status and likelihood of COVID-19 testing, risk of infection, and risk of hospitalization. For example, if unvaccinated individuals are also tested for infection less frequently, this will tend to bias the estimated efficacy rate against infection downward. A similar downward bias is possible if vaccinated individuals tend to have contact with more COVID-19-infected individuals than unvaccinated individuals do. Positive biases are possible as well—for example, if vaccination status is positively correlated with other behaviors such as masking and adherence to social distancing that make the vaccinated individuals less susceptible to infection for reasons unrelated to their vaccination status.

Vaccine efficacy rates in the study are estimated using Cox regression models, which estimate the probability of infection and hospitalization conditional on vaccination status, time since vaccina-

tion, and other environmental and individual controls. Over the entire study period, the estimated overall efficacy rate against infection is 73 percent (CI: 72–74 percent) and against COVID-19-related hospitalization is 90 percent (CI: 89–92 percent), which is broadly consistent with the other studies. Efficacy against infection is declining in age, with the higher efficacy for adults age 16–44 and 45–64 (73 percent, CI: 71–74 percent for both subpopulations) than for adults age 65 and older (61 percent, CI: 57–65 percent). However, efficacy against hospitalization remains more or less constant across age groups, with 92 percent efficacy (CI: 88–95 percent) for adults age 16–44, 91 percent efficacy (CI: 88–93 percent) for those age 45–64, and 86 percent efficacy (CI: 82–88 percent) for adults age 65 and older.

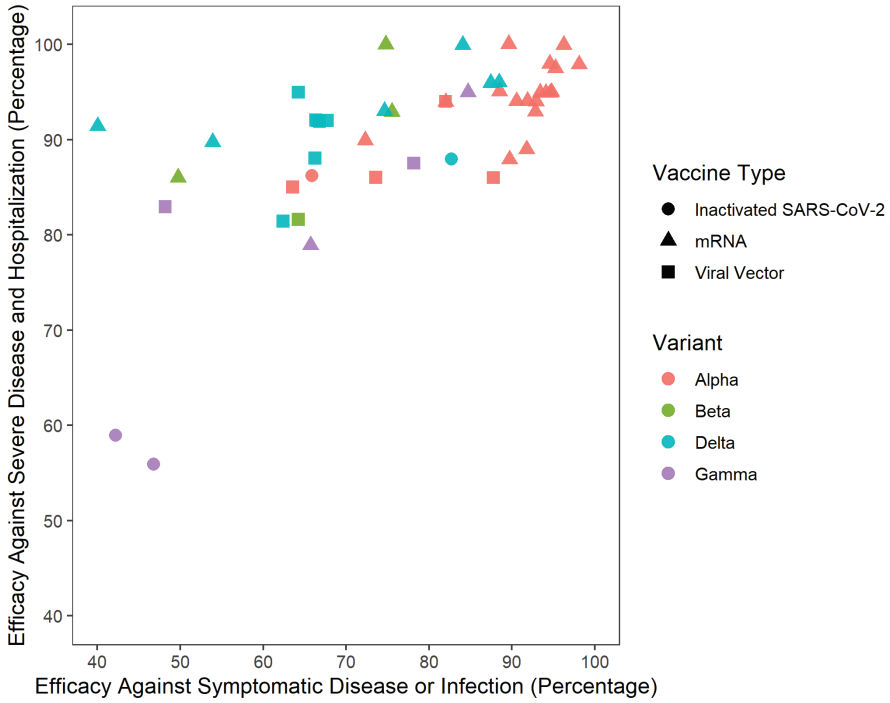
The authors also find that vaccine efficacy against infection declines from 88 percent (CI: 86–89 percent) during the first month after vaccination to 47 percent (CI: 43–51 percent) five or more months post-vaccination. However, efficacy against hospitalization remains nearly constant over the entire period. Further, the waning effectiveness against infection does not appear related to any particular COVID-19 variant.

A Summary of Efficacy Rates Against Virus Variants

A key question for policymakers is whether the available vaccines' efficacy varies with each wave of a new COVID-19 variant. The delta variant, for example, accounted for less than 7 percent of COVID-19 cases in the country at the end of May 2021 but quickly rose to over half of all cases just one month later, and it now accounts for nearly all new COVID-19 infections (Our World in Data 2021b). Whether the vaccines provide equal protection against emerging variants will inform, for example, whether variant-specific booster shots will be required in the future to maintain protection against the evolving virus and which virus strains are likely to become predominant as vaccination rates around the world continue to climb.

A recent meta-analysis by Philip Krause et al. (2021) offers a summary of the rates of protection provided against different variants across the globe. The authors compiled the results from multiple randomized controlled trials and studies based on observational data. Figure 1 displays the effectiveness against both severe disease/hospitalization and symptomatic disease/infection of different

Figure 1. Vaccine Efficacy by Variant and Vaccine Type—Multiple Studies



Source: Authors, based off Krause et al. (2021).

vaccines against different variants in 47 different studies listed in the technical appendix of Krause et al. (2021). We remove studies in which data were not available for efficacy against both severe disease/hospitalization and symptomatic disease/infection. The 47 studies were conducted in 12 countries, and 31 of the studies were conducted in Canada, Israel, the UK, or the US.

As Figure 1 shows, efficacy against both symptomatic disease/infection and against severe disease/hospitalization appears strongest against the alpha variant. The mRNA and viral vector–based vaccines also appear to be as effective in preventing severe infection/hospitalization against the beta and delta variants.

The vaccines may be less effective, however, in preventing symptomatic disease/infection against more recent variants. The meta-analysis in Krause et al. (2021) finds that current vaccines have efficacy rates of 74.1 percent (CI: 70.5–77.8 percent) against beta and 82.6 percent (CI: 81.4–83.9 percent) against delta, compared with 92.2 percent (CI: 91.9–92.4 percent) against alpha, which is consistent with both the lower average efficacy and wider range of efficacy estimates in Figure 1.

International Vaccine Efficacy

The US has relied heavily on the two mRNA vaccines that were fast-tracked by Operation Warp Speed (OWS) contracts, but many other countries, especially those considered in the middle- and low-income tiers, are deploying five inoculations that rely on older technologies, including two sponsored by China and one by Russia. The relative efficacy of these vaccines will be important for the future trajectory of the pandemic because of their wide dissemination globally.

Oxford-AstraZeneca. Early in the pandemic, the Oxford-AstraZeneca vaccine candidate was considered a front-runner for use both in Western countries and throughout the world because of its low cost and the expectation that the technology it was using would be reliable. The US made the purchase of hundreds of millions of these vaccines a top priority in the first rounds of OWS investments. However, after broad publicity around rare adverse events, demand in the West for the vaccine fell precipitously. Many European countries have deployed it with conditions, but its use has been far below what was initially expected (except in the UK, which has given this vaccine to a large segment of its population).

Despite the tepid uptake in the West, this vaccine is still a major component of the global vaccination campaign. It relies on an adenovirus vector to deliver the genetic instructions for the SARS-CoV-2 spike protein to human cells, which then produce the protein that induces an associated immune response. The World Health Organization (WHO) approved the vaccine for emergency use in February 2021.

BBIBP-CorV. The Chinese state-owned drug firm, Sinopharm, developed a vaccine using a deactivated virus methodology. The company replicated samples of the virus in a laboratory and then used a chemical process to deactivate its potency. Particles from the spike protein are then used in the vaccine to induce an immune response in vaccine recipients. The WHO approved the Sinopharm vaccine for emergency use in May 2021.

CoronaVac. The Chinese biotech firm Sinovac developed the CoronaVac candidate using a similar deactivated virus methodology to the BBIBP-CorV vaccine. The WHO approved it for emergency use in June 2021.

Sputnik V. The Russian Ministry of Health, through the Gamaleya Research Institute of Epidemiology and Microbiology, developed a vaccine that uses a similar technology as the Oxford-AstraZeneca shot. Despite its widespread use globally, the WHO has still not approved it for emergency use, partly because of continued concerns about the integrity of the manufacturing process being used to scale its production.

Johnson & Johnson. The Johnson & Johnson vaccine—also using an adenovirus vector technology—has been approved by the WHO for emergency use and has been taken up in many countries around the world, including in the US. However, manufacturing problems and questions about adverse events have lessened the demand for it,

and it has not yet been a major factor in the global vaccination campaign.

Efficacy Evaluations. Like the Pfizer-BioNTech and Moderna shots, the deployment of these vaccines around the world has led to a large number of evaluations based on real-world data. These studies come with the same issues related to nonrandom selection into treatment, correlations between treatment status and COVID-19 testing frequency, and other general concerns about data quality as those used to assess the mRNA vaccines in the US.

Oxford-AstraZeneca. Jamie Lopez Bernal et al. (2021) use a test-negative study design to assess the efficacy of the Oxford-AstraZeneca vaccine against symptomatic COVID-19 resulting from either the alpha or the delta variant. They gathered data on all COVID-19 test results in the UK recorded by hospitals or public health laboratories where the person reported symptoms and received a test within 10 days of the onset of those symptoms. Data were collected between October 26, 2020, and May 16, 2021, resulting in 14,837 observations of the alpha variant and 4,272 observations of the delta variant. The authors find the Oxford-AstraZeneca vaccine 74.5 percent (CI: 68.4–79.4 percent) effective against symptomatic disease caused by the alpha variant and 67.0 percent (CI: 61.3–71.8 percent) effective against the delta variant.

BIBBP-CorV and CoronaVac. Min Kang et al. (2021) carry out a retrospective cohort analysis in May and June 2021, after a COVID-19 outbreak identified in Guangdong, China, caused by the delta variant. The study included all "close contacts" of confirmed cases in the city, resulting in a sample size of 10,813 people, of whom 1,407 were fully vaccinated. All but four of those who were fully vaccinated had either the BIBBP-CorV or CoronaVac vaccine, and the remaining four received a similar inactivated vaccine. They find 69.5 percent (CI: 42.8–96.3 percent) vaccine efficacy against COVID-19 pneumonia for fully vaccinated individuals and near-zero efficacy for those with a single dose of the inactivated vaccines (8.4 percent, CI: –47.6–64.4 percent).

Sputnik V. Anton Barchuk et al. (2021) use a case-control study in St. Petersburg, Russia, to assess the efficacy of the Sputnik V vaccine against hospitalization from COVID-19. Using the triage system for symptomatic COVID-19 patients set up in St. Petersburg that tests and determines whether a patient should be hospitalized, Barchuk et al. (2021) define the case group as those who are hospitalized and the control group as those who are not. Efficacy rates are estimated from a sample of 13,893 symptomatic COVID-19 patients collected from July 3, 2021, to August 9, 2021. The study finds that two doses of Sputnik V, the full vaccination amount, is 81 percent (CI: 68–88 percent) effective at preventing hospitalization in COVID-19 patients. The efficacy reduces to approximately 35 percent (CI: –21–65 percent) for those with only one dose of the vaccine.

Discussion and Context

When the two US-approved mRNA candidates were studied in carefully designed trials, their efficacy rates against symptomatic COVID-19 infection were above 90 percent. Recent real-world data are signaling some erosion may have occurred over time and in the face of variants that have become dominant this year, although the mRNA vaccines' efficacy against serious disease remains high.

If true, the slight downgrading of the efficacy of the vaccines could have implications for the potential introduction of boosters, new versions of the vaccines with tweaks for addressing the newly circulating strains, and expectations about the likelihood of a vaccinated person passing the virus to others.

While all these implications are possible, it is important to not overreact to statistical evidence that should be understood in context. In particular, there are several reasons to believe that real-world assessment of vaccine efficacy, at this stage of the pandemic, may understate their actual effectiveness.

First, the "control group" in real-world assessments—that is, those who remain unvaccinated—may have higher levels of natural, and undetected, immunity from prior COVID-19 infections. If so, they may be less susceptible to symptomatic infection and certainly less likely to be hospitalized from a reinfection. Therefore, the incident rate against which vaccination efficacy is measured is

likely to trend downward over time as a larger proportion of the unvaccinated become infected and acquire immunity.

Second, sources of random error in real-world assessment, including false-positive and false-negative tests for COVID-19, and errors in determining vaccination status tend to bias estimates of vaccine efficacy toward zero. Grannis et al. (2021) report estimates from a simulation study in which the true vaccine efficacy is 95 percent and errors in testing and vaccination classification were consistent with studies from prior vaccination efforts. They find that their expected observed vaccine efficacy given these data errors declines to 85 percent, with larger biases possible depending on the true efficacy rate, the probability of being hospitalized conditional on a COVID-19 infection, and the extent of these testing and vaccination classification errors.

Third, unobservable behavioral differences between vaccinated and unvaccinated adults could create a correlation between vaccination status and the likelihood of COVID-19 infection that is unrelated to the vaccine itself. If more vaccinated adults than unvaccinated adults engage in activities that make them more likely to contract COVID-19, then observational studies would understate the efficacy of the vaccine. In contrast, if vaccinated adults refrain from activities that make them likely to contract COVID-19, observational studies would overstate the efficacy of the vaccine. For different subpopulations, both effects are possible, and the effect may have changed over time. For example, if vaccinated adults have begun to engage in more activities that put them at a higher risk of contracting COVID-19 as (1) they have become more confident in the efficacy of the vaccines and (2) public health guidance has loosened, this could produce a downward trend in vaccine efficacy rates in observational data over time.

Despite the imperfections of studies relying on real-world data, policymakers do not have the luxury to ignore them or wish for more certainty around the information they must use to make decisions. A pandemic is a public emergency, which requires rapid decision-making based on the best available data, imperfect as they may be.

That being the case, the information that has been accumulated over the past year, after approval of the vaccines for emergency use, points toward certain broad conclusions.

First, the mRNA vaccines have been highly effective in protecting the population receiving them, and only now barely detectable indications of erosion are emerging. For caution's sake, a booster program may be advisable, but delaying it for healthy patients is unlikely to carry substantial risks. A much higher priority is getting first doses to those who have not been vaccinated at all, both in the US and globally.

Second, being vaccinated by any of the available vaccines is much better than not being vaccinated, although the inactivated virus vaccines produced in China appear to require two doses to be effective at all and are much less effective than the mRNA vaccines are. Their efficacy should be monitored carefully, as the immunity they confer could either fade rapidly or be too weak for a new variant that emerges.

The advent of effective vaccines ushered in a distinct and more hopeful stage in the global pandemic, as the approved inoculations provide substantial protection against the worst consequences of COVID-19 disease. Careful statistical analysis during the trial phase helped demonstrate their value. The same care when collecting and assessing post-approval data can steer the world through the coming months as policymakers weigh what the next steps should be for ending the crisis.

About the Authors

James C. Capretta is a senior fellow and holds the Milton Friedman Chair at the American Enterprise Institute.

Scott Ganz is a research fellow in economic policy studies at the American Enterprise Institute.

Kieran Allsop is a research associate at the American Enterprise Institute.

References

Barchuk, Anton, Mikhail Cherkashin, Anna Bulina, Natalia Berezina, Tatyana Rakova, Darya Kuplevatskaya, Oksana Stanevich, Dmitriy Skougarevskiy, and Artemiy Okhotin. 2021. "Vaccine Effectiveness Against Referral to Hospital and Severe Lung Injury Associated with COVID-19: A Population-Based Case-Control Study in St. Petersburg, Russia." medRxiv. September 3. https://doi.org/10.1101/2021.08.18.21262065.

Fowlkes, Ashley, Manjusha Gaglani, Kimberly Groover, Matthew S. Thiese, Harmony Tyner, and Katherine Ellingson. 2021. "Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance—Eight U.S. Locations, December 2020–August 2021." *Morbidity and Mortality Weekly Report* 70, no. 34 (August 27): 1167–69. http://dx.doi.org/10.15585/mmwr.mm7034e4.

Grannis, Shaun J., Elizabeth A. Rowley, Toan C. Ong, Edward Stenehjem, Nicola P. Klein, Malini B. DeSilva, Allison L. Naleway, Karthik Natarajan, and Mark G. Thompson. 2021. "Interim Estimates of COVID-19 Vaccine Effectiveness Against COVID-19—Associated Emergency Department or Urgent Care Clinic Encounters and Hospitalizations Among Adults During SARS-CoV-2 B.1.717.2 (Delta) Variant Predominance—Nine States, June–August 2021." *Morbidity and Mortality Weekly Report* 70, no. 37 (September 17): 1291–93. http://dx.doi.org/10.15585/mmwr.mm7037e2.

Kang, Min, Yao Yi, Yan Li, Limei Sun, Aiping Deng, Ting Hu, Jiayi Zhang, Jun Liu, Mingji Cheng, Shen Xie, Min Luo, Jing Jiang, Yawen Jiang, Shixing Tang, and Jianfeng He. 2021. "Effectiveness of Inactivated COVID-19 Vaccines Against COVID-19 Pneumonia and Severe Illness Caused by the B.1.617.2 (Delta) Variant: Evidence from an Outbreak in Guangdong, China." *Lancet* (August 5). http://dx.doi.org/10.2139/ssrn.3895639.

Krause, Philip R., Thomas R. Fleming, Richard Peto, Ira M. Longini, Peter Figueroa, Jonathan A. C. Sterne, Alejandro Cravioto, Helen Rees, Julian P. T. Higgins, Isabelle Boutron, Hongchao Pan, Marion F. Gruber, Narendra Arora, Fatema Kazi, Rogerio Gaspar, Soumya Swaminathan, Michael J. Ryan, and Ana-Maria Henao-Restrepo. 2021. "Considerations in Boosting COVID-19 Vaccine Immune Responses." *Lancet* (September 13). https://doi.org/10.1016/S0140-6736(21)02046-8.

Lopez Bernal, Jamie, Nick Andrews, Charlotte Gower, Eileen Gallagher, Ruth Simmons, Simon Thelwall, Jlia Stowe, Elise Tessier, Natalie Groves, Richard Myers, Colin N. J. Campbell, Gayatri Amirthalingam, Matt Edmunds, Maria Zambon, Kevin E. Brown, Susan Hopkins, Meera Chand, and Mary Ramsay. 2021. "Effectiveness of Covid-19 Vaccines Against the B.1.617.2 (Delta) Variant." *New England Journal of Medicine* 385, no. 7 (August 12): 585–94. https://doi.org/10.1056/NEJMoa2108891.

Our World in Data. 2021a. "Coronavirus (COVID-19) Vaccinations." https://ourworldindata.org/covid-vaccinations.

Our World in Data. 2021b. "SARS-CoV-2 Variants in Analyzed Sequences, United States." https://ourworldindata.org/grapher/covid-variants-area?country=~USA.

Puranik, Arjun, Patrick J. Lenehan, Eli Silvert, Michiel J. M. Niesen, Juan Corchado-Garcia, John C. O'Horo, Abinash Virk, Melanie D. Swift, John Halamka, Andrew D. Badley, A. J. Venkatakrishnan, and Venky Soundararajan. 2021. "Comparison of Two Highly-Effective mRNA Vaccines for COVID-19 During Periods of Alpha and Delta Variant Prevalence." medRxiv. August 8. https://doi.org/10.1101/2021.08.06.21261707.

Self, Wesley H., Mark W. Tenforde, Jillian P. Rhoads, Manjusha Gaglani, Adit A. Ginde, David J. Douin, Samantha M. Olson, H. Keipp Talbot, Jonathan D. Casey, Nicholas M. Mohr, Anne Zepeski, Tresa McNeal, Shekhar Ghamande, Kevin W. Gibbs, D. Clark Files, David N. Hager, Arber Shehu, Matthew E. Prekker, Heidi L. Erickson, Michelle N. Gong, Amira Mohamed, Daniel J. Henning, Jay S. Steingrub, Ithan D. Peltan, Samuel M. Brown, Emily T. Martin, Arnold S. Monto, Akram Khan, Catherine L. Hough, Laurence W. Busse, Caitlin C. ten Lohuis, Abhijit Duggal, Jennifer G. Wilson, Alexandra June Gordon, Nida Qadir, Steven Y. Chang, Christopher Mallow, Carolina Rivas, Hilary M. Babcock, Jennie H. Kwon, Matthew C. Exline, Natasha Halasa, James D. Chappell, Adam S. Lauring, Carlos G. Grijalva, Todd W. Rice, Ian D. Jones, William B. Stubblefield, Adrienne Baughman, Kelsey N. Womack, Christopher J. Lindsell, Kimberly W. Hart, Yuwei Zhu, Lisa Mills, Sandra N. Lester, Megan M. Stumpf, Eric A. Naioti, Miwako Kobayashi, Jennifer R. Verani, Natalie J. Thornburg, and Manish M. Patel. 2021. "Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among

Adults Without Immunocompromising Conditions—United States, March–August 2021." *Morbidity and Mortality Weekly Report* 70, no. 38 (September 24): 1337–43. http://dx.doi.org/10.15585/mmwr.mm7038e1.

Tartof, Sara Y., Jeff M. Slezak, Heidi Fischer, Vennis Hong, Bradley K. Ackerson, Omesh N. Ranasinghe, Timothy B. Frankland, Oluwaseye A. Ogun, Joann M. Zamparo, Sharon Gray, Srinivas R. Valluri, Kaije Pan, Frederick J. Angulo, Luis Jodar, and John M. McLaughlin. 2021. "Effectiveness of mRNA BNT162b2 COVID-19 Vaccine up to 6 Months in a Large Integrated Health System in the USA: A Retrospective Cohort Study." *Lancet* (October 4). https://doi.org/10.1016/S0140-6736(21)02183-8.

Thompson, Mark G., Edward Stenehjem, Shaun Grannis, Sarah W. Ball, Allison L. Naleway, Toan C. Ong, Malini B. DeSilva, Karthik Natarajan, Catherine H. Bozio, Ned Lewis, Kristin Dascomb, Brian E. Dixon, Rebecca J. Birch, Stephanie A. Irving, Suchitra Rao, Elyse Kharbanda, Jungmi Han, Sue Reynolds, Kristin Goddard, Nancy Grisel, William F. Fadel, Matthew E. Levy, Jill Ferdinands, Bruce Fireman, Julie Arndorfer, Nimish R. Valvi, Elizabeth A. Rowley, Palak Patel, Ousseny Zerbo, Eric P. Griggs, Rachael M. Porter, Maria Demarco, Lenee Blanton, Andrea Steffens, Yan Zhuang, Natalie Olson, Michelle Barron, Patricia Shifflett, Stephanie J. Schrag, Jennifer R. Verani, Alicia Fry, Manjusha Gaglani, Eduardo Azziz-Baumgartner, and Nicola P. Klein. 2021. "Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings." *New England Journal of Medicine* (September 8). https://doi.org/10.1056/NEJMoa2110362.