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Long-term Protection Associated With COVID-19 Vaccination and Prior Infection

Mark W. Tenforde, MD, PhD,
Ruth Link-Gelles, PhD,
Manish M. Patel, MD

CDC COVID-19 Response Team, Centers for Disease Control and Prevention, Atlanta, Georgia.

COVID-19 vaccines are considered to have prevented an estimated tens of millions of SARS-CoV-2 infections and tens of thousands of COVID-19–related deaths in the US.[1]However, the combination of reduced vaccine effectiveness against infection in the setting of Omicron sublineages and increased vaccination coverage[2] has resulted in an increasing number of cases among vaccinated individuals. Designing and interpreting postauthorization, observational COVID-19 vaccine effectiveness studies have also become increasingly complex due to effects of prior infection on the risk and severity of repeat infections, emergence of variants that evade vaccine-induced immunity, waning immunity, more vaccine products and dosing schedules, and heterogeneity in outcomes measured within and across studies. The proper design and interpretation of vaccine effectiveness studies have consequences for vaccine research and policy decisions and for the public's perception and trust of vaccines.

COVID-19 vaccine effectiveness should be considered in the context of infection history and exposure groups being compared. Most people in the US have immunity against SARS-CoV-2 from prior vaccination, infection, or both (ie, hybrid immunity).[3,4] Cohort and test-negative case-control studies have demonstrated that prior infection alone is associated with a reduced riskofreinfection.[5,6] Many infections are not captured in available data sources due to lack of symptoms, lack of testing, or increasing use of unreported at hometests.[7]COVID-19 vaccine effectiveness studies often measure the association between COVID-19 risk and vaccination using an unvaccinated reference group (also referred to as "absolute" estimated vaccine effectiveness). Studies that compare risk of COVID-19 in vaccinated and unvaccinated groups may find lower absolute vaccine effectiveness compared with early time periods now that unvaccinated individuals are more likely to have experienced prior infection and have some degree of immunity for a period after infection. However, infections also occur among vaccinated persons and might provide hybrid immunity with better protection than infection in unvaccinated persons. Thus, absolute vaccine effectiveness remains an important measure because it provides a snapshot

Corresponding Author: Mark W. Tenforde, MD, PhD, Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mailstop H24-7, Atlanta, GA 30329 (pij6@cdc.gov).

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of vaccination benefits in the context of increasingly complicated vaccination and infection histories.

An alternative method of evaluating effectiveness is “relative” estimated vaccine effectiveness, which assesses the association between COVID-19 risk and vaccination status among different vaccinated groups, eg, boosting after a primary vaccine series vs a primary vaccine series alone. Relative vaccine effectiveness evaluations are useful in highly vaccinated populations (eg, older adults or settings that have high vaccination coverage), in instances in which unvaccinated and vaccinated groups are highly different in ways not captured in available data sources, and for policy decisions focused on benefits of additional vaccine doses among previously vaccinated populations.[8] Relative vaccine effectiveness estimates provide distinct and complementary results to absolute vaccine effectiveness.

Additional challenges in vaccine effectiveness studies include disentangling effects of newer SARS-CoV-2 variants with increased immune evasion from effects of waning of protection and from host factors that may modify immune responses.[9,10] The SARS-CoV-2 Omicron variant emerged in November 2021 and quickly became the predominant circulating variant globally due to high transmissibility and increased immune evasion compared with the previously predominant Delta variant.[11] Omicron subvariants, including the now-predominant BA.5, have demonstrated further potential for immune evasion against first-generation COVID-19 vaccines, which target the ancestral strain of SARS-CoV-2.[12] Similarly, waning immunity is also expected in many US adults who completed a primary COVID-19 vaccine series more than 1 year ago. Vaccine effectiveness studies seek to discriminate effects of virus strain from host effects through stratifying vaccine effectiveness by variant period and by time since vaccination within a defined calendar period. Ideally, these evaluations should account for additional baseline host characteristics. For example, people with immunocompromising conditions may have a suboptimal immune response to vaccination; immunosenescence in older adults may also affect vaccine response and the durability of protection. The staggered timing of vaccine authorizations, including earlier rollout in high-risk populations, might result in spuriously lower vaccine effectiveness, when this finding may be due instead to waning immunity among people first prioritized for COVID-19 vaccination. Capturing the spectrum of disease severity among those hospitalized with COVID-19 might also be useful for understanding heterogeneity in vaccine effectiveness. Some hospitalizations might be related to milder SARS-CoV-2 infection in hosts with complex underlying conditions compared with COVID-19–related acute lung injury.

In this issue of *JAMA*, Lin et al describe a cohort study of 10.6 million people in North Carolina that attempts to disentangle effects of primary and booster vaccination from prior infection.[13] The authors include an observation period spanning several variant periods and evaluate protection against a spectrum of infection severity. Patient demographic characteristics, vaccination history, and SARS-CoV-2 laboratory testing were linked using statewide registries, although many baseline clinical characteristics of individuals were unavailable and outcome measures were missing in a high proportion of patients. The authors evaluated the association between primary series vaccination or prior infection and infection or disease, compared with the unvaccinated state; they also assessed relative

vaccine effectiveness by evaluating the association between booster vaccination with or without prior infection, compared with a primary vaccination series alone.

The authors report that as of June 3, 2022, a total of 67% of the study population had been vaccinated and 2771364 SARS-CoV-2 infections were reported, with a hospitalization rate of 6.3% and mortality rate of 1.4%. Based on the analysis and findings, there are several important takeaways from this study. First, the results reinforced that first-generation COVID-19 vaccines were highly and durably effective against severe disease as measured by hospitalizations and deaths, but did not protect against milder infections beyond a few months, even with booster vaccinations. Emerging new variants, including Omicron, are associated with less protection against infection. However, even modest protection against SARS-CoV-2 infection may provide important benefits by reducing surges that can overwhelm health care systems, keeping schools and workplaces open, and protecting vulnerable populations at risk for severe outcomes following infection, including older adults and those with underlying medical conditions.

Second, prior infection was associated with a reduction in risk of infection and severe outcomes among those with or without prior vaccination. Additionally, among people with prior documented infection who had completed a primary vaccine series, booster vaccination was associated with additional protection, including 39.3% vaccine effectiveness against hospitalization after 3 months. Although prior infection alone is associated with lower risk of reinfection, vaccination also provides protection against ongoing transmission and has additional benefits, including attenuating severity of disease and reducing the risk of disabling postacute sequelae of COVID-19.[9,14]

Third, this study reinforced the growing complexities of COVID-19 and the strengths and limitations of routine surveillance systems. State-based surveillance systems have large sample sizes that allow detection of uncommon events and multiple subgroup analyses. However, they often lack granular details on underlying medical conditions or other factors that allow for better control of confounding or effect modification. Lin et al found that waning of booster dose vaccine Effectiveness occurred over 4 to 6 months, but this may be partially due to patients with certain high-risk conditions, such as those who are significantly immunocompromised, getting third doses earlier than the general population. Among individuals who received a primary mRNA vaccine series, understanding comparability between those who received homologous and heterologous mRNA boosters would also be helpful to strengthen inference a round benefits of receiving mixed vaccine products that was observed in this study.

Considering these growing complexities, developing the best strategies to reduce the morbidity and mortality associated with future COVID-19 surges warrants a strategic approach to monitor vaccine effectiveness. Monitoring will require complementary surveillance systems that can generate timely vaccine effectiveness estimates with accuracy and precision to guide policies and research. Large routinely collected surveillance data linked with vaccination records have been useful for monitoring of vaccination effects early in the pandemic, when effectiveness against infection was high and most of the population had not been infected. As new variants have emerged, protection against

infection has declined and vaccination schedules have become more complicated (eg, different recommendations by underlying health condition); case surveillance data have important strengths but also limitations. Thus, additional enhanced surveillance systems that integrate laboratory reporting (including sequencing and prior results from the patient) and detailed clinical data are also important to disentangle the relationships of repeat infections, waning, and immune evasion with outcomes. Careful monitoring is needed to generate accurate vaccine effectiveness estimates because each of these causes of potential declines in vaccine effectiveness can have implications for vaccine policy.

As the pandemic continues, new variants will likely emerge and new vaccines will become available, including multivalent, mucosal, and universal coronavirus vaccines. For instance, on August 31, 2022, 2 new bivalent COVID-19 vaccines (ie, “updated boosters”) that include 2 mRNA components of the SARS-CoV-2 virus were authorized by the US Food and Drug Administration. Just as with prevention measures, strong and overlapping surveillance and research platforms are needed to ensure timely understanding of the strengths and weaknesses of these and other new vaccine preparations; to understand how effective COVID-19 vaccines are against new variants; and to provide direction for future policy considerations, such as preferential recommendations for certain people such as those with immunocompromising or other complex medical conditions and timing of booster doses.

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