THE BEST OF THE WEEK (15 mag – 21 mag 2023)

Francesco Menegale et al

Evaluation of Waning of SARS-CoV-2 Vaccine–Induced Immunity

A Systematic Review and Meta-analysis

JAMA, May 2023; doi:10.1001/jamanetworkopen.2023.10650

Abstract

Importance Estimates of the rate of waning of vaccine effectiveness (VE) against COVID-19 are key to assess population levels of protection and future needs for booster doses to face the resurgence of epidemic waves.

Objective To quantify the progressive waning of VE associated with the Delta and Omicron variants of SARS-CoV-2 by number of received doses.

Data Sources PubMed and Web of Science were searched from the databases' inception to October 19, 2022, as well as reference lists of eligible articles. Preprints were included.

Study Selection Selected studies for this systematic review and meta-analysis were original articles reporting estimates of VE over time against laboratory-confirmed SARS-CoV-2 infection and symptomatic disease.

Data Extraction and Synthesis Estimates of VE at different time points from vaccination were retrieved from original studies. A secondary data analysis was performed to project VE at any time from last dose administration, improving the comparability across different studies and between the 2 considered variants. Pooled estimates were obtained from random-effects meta-analysis.

Main Outcomes and Measures Outcomes were VE against laboratory-confirmed Omicron or Delta infection and symptomatic disease and half-life and waning rate associated with vaccine-induced protection.

Results A total of 799 original articles and 149 reviews published in peer-reviewed journals and 35 preprints were identified. Of these, 40 studies were included in the analysis. Pooled estimates of VE of a primary vaccination cycle against laboratory-confirmed Omicron infection and symptomatic disease were both lower than 20% at 6 months from last dose administration. Booster doses restored VE to levels comparable to those acquired soon after the administration of the primary cycle. However, 9 months after booster administration, VE against Omicron was lower than 30% against laboratory-confirmed infection and symptomatic disease. The half-life of VE against symptomatic infection was estimated to be

87 days (95% CI, 67-129 days) for Omicron compared with 316 days (95% CI, 240-470 days) for Delta. Similar waning rates of VE were found for different age segments of the population.

Conclusions and Relevance These findings suggest that the effectiveness of COVID-19 vaccines against laboratory-confirmed Omicron or Delta infection and symptomatic disease rapidly wanes over time after the primary vaccination cycle and booster dose. These results can inform the design of appropriate targets and timing for future vaccination programs.

Janko Ž. Nikolich, and Clifford J. Rosen

Toward Comprehensive Care for Long Covid

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Abstract

Three years into the Covid pandemic, SARS-CoV-2 is still with us. As the virus evolves, it continues to pose a health threat in terms of both acute infections (or reinfections) and postacute sequelae. In regard to the former, there is evidence that several pharmacologic interventions reduce the severity of infections, lessen morbidity, and lower mortality. Prevention programs have also been successful in reducing overall infection rates. These efforts can be traced in part to colossal federal support for work ranging from vaccine development to clinical trials to nationwide educational endeavors. Such impressive support is all the more striking in contrast to the void in patient care for a SARS-CoV-2 postviral syndrome that may affect 10% or more of infected people.1,2

The sequelae of SARS-CoV-2 infection can involve multiple organ systems and are often grouped together as “long Covid” or PASC (postacute sequelae of SARS-CoV-2).3 But the terms themselves are nebulous, the clinical presentations extremely variable, and the prognosis uncertain.4,5 The absence of evidence-based treatments further fuels the frustration of affected patients and their clinicians. Add to these problems our shaky and fragmented health care system, additionally wobbled by the pandemic, and the result is disarray in our approach to this complex and multifaceted disorder.

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The extent of the symptom complex of long Covid is unknown, in part because there is no well-accepted definition of the syndrome and because of the relatively poor penetration of care to marginalized populations that have been disproportionately affected by the pandemic. The Centers for Disease Control and Prevention (CDC) defines long Covid as a wide range of new, returning, or ongoing health problems occurring more than 4 weeks after someone becomes infected with SARS-CoV-2. The World Health Organization (WHO) does not fully define long Covid but classifies it by continuation or onset of new symptoms 3 months after the original bout of illness or positive test.

In October 2021, the world adopted International Classification of Diseases code U09.9 to help clinicians document visits of patients with long Covid. Basically, one or multiple symptoms persisting or occurring more than 4 weeks after the onset of acute SARS-CoV-2 infection are coded as U09.9. Signs and symptoms include shortness of breath, fatigue with or without exertion, myalgia, glucose intolerance, multisystem inflammatory syndrome, postural orthostatic tachycardia, peripheral neuropathy, and others reflective of multi–organ-system involvement.4,5 Although this categorization is helpful for research and tracking of electronic health records, it does little to help clinicians or affected people make their way through a maze of difficulties from diagnosis to treatment.

The pathophysiology of long Covid remains elusive, in part because of the multiple possible signs, symptoms, and organ systems involved.3 A lack of understanding of long Covid inevitably also complicates care. Long Covid clinics have been established to provide multidisciplinary care, although most affected patients are also followed by primary care providers or seen by various specialists, depending on the duration and severity of their dominant symptoms. Educational programs for patients and clinicians are lacking. Referrals to subspecialists such as cardiologists, pulmonologists, and neurologists are common but often lead to more delays, fragmentation of care, and frustration at all levels. Primary care providers feel the brunt of that frustration, both their patients' and their own at their inability to help beyond deploying simple strategies, such as exercise or nutritional supplementation, that are used as preventive measures for healthy people.

Patients with long Covid are still subject to stigmatization because of perceived simulation or psychosomatization of symptoms. And most people with long Covid do not feel empowered to take control of their care. At the state and local levels, referral centers that focus on long Covid management are not only sparse and unevenly distributed, but also generally overbooked, difficult to access, and frequently far from patients' homes. Moreover, there are few or no available treatment options that have been rigorously tested in clinical trials.

On the national level, as part of the initial federal response to long Covid, the National Institutes of Health launched the Researching COVID to Enhance Recovery (RECOVER) initiative (in which we are investigators), which selected a network of enrollment sites (hubs) that cover adults, pregnant people, and children in 33 states, the District of Columbia, and Puerto Rico. In the initial phase of RECOVER, each adult hub worked with community partners to enroll more than 12,000 participants whose clinical tests and data on characteristics are collected in associated biobanks and databases. The goal of adult RECOVER is threefold: to define the clinical spectrum and pathophysiology of long Covid, to determine its natural history and prevalence, and to characterize the way in which SARS-CoV-2 causes postacute sequelae.

In the adult RECOVER longitudinal study, the vast majority of participants were infected with SARS-CoV-2, although a small percentage were recruited as uninfected controls. Some but not all continue to have chronic sequelae from that infection. The second phase of adult RECOVER will involve a limited number of clinical trials for patients with long Covid. Similar trials are planned for RECOVER's child cohort. In our view, this research initiative is comprehensive and scientifically sound. But many participants have conveyed to investigators their frustration with the fact

that delivery of both their primary and specialty health care is, at best, dissociated from RECOVER and in many cases is fragmented, poorly coordinated, or even nonexistent.

RECOVER is a building block for ultimately establishing the clinical definition of long Covid. We believe that over and above this research effort, the country needs additional structures that can provide the capacity for clinicians, patients, caregivers, advocacy groups, employers, and government officials to learn about, adapt, and implement interventions, therapeutics, and other best practices to combat long Covid.

We suggest that this effort include several key features. First, it should support people with long Covid by coordinating clinical care and rehabilitation, reducing health care disparities, and addressing ongoing and complex medical and psychosocial needs, with a particular focus on patients who currently receive fragmented care or no care at all. Such support could be provided by means of national long Covidcenters of excellence. This program could begin by building out some centers involved in RECOVER so that they not only collect data and follow participants, but also provide comprehensive care for those patients and others with long Covid. RECOVER serves a cross section of underserved communities through research centers in both urban and rural areas and can act as a bridge to care provision for these patients.

Second, we need to define, continuously improve, and implement standards of care and best practices, built on evidence obtained through a coordinated exchange of information. Third, we can leverage innovative methods for disseminating information and providing support in order to educate clinicians, patients, and communities; broaden access to high-quality care; and further reduce disparities. And fourth, we will need to develop and implement workforce training programs for clinicians caring for patients with long Covid.

To implement such an ambitious program, we strongly urge Congress to consider appropriating funding in fiscal year 2024 for the Health Resources and Services Administration to competitively select centers of excellence in long Covid care by leveraging and expanding the initial investment in RECOVER hubs and other federally supported long Covid activities.

In addition, such centers could support and leverage, both nationally and throughout their states, greater educational initiatives from the CDC and the WHO for both clinicians and patients. Some examples include continuing education programs, grand rounds, and the Project ECHO (Extension for Community Healthcare Outcomes) model, a scalable and effective way of using electronic media to inform and facilitate changes in health and education for clinicians. These efforts should focus on symptom complexes, potential complications, and management strategies. We need to demystify the disease and empower affected people, involving them actively in their own care and in education and training. We also recommend that insurance providers reexamine criteria for disability claims and urge employers to gain a better understanding of this disorder and its wide-ranging implications. Most important, we need to put people and communities, not diseases, at the center of our health systems and empower them to take charge of their own health rather than be passive recipients of services.

If the prevalence of long Covid is indeed between 5 and 15%, we will continue to face an enormous challenge to our national health and our health care system moving forward. Innovative approaches will be needed to care for patients with long Covid, and these need to be backed by education, research, and support at all levels. It'sabout time.

Dan-Yu Lin et al.

Durability of Bivalent Boosters against Omicron Subvariants

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Abstract

On September 1, 2022, the Moderna and Pfizer–BioNTech bivalent vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) containing equal amounts of spike messenger RNA from the ancestral and omicron BA.4–BA.5 subvariants replaced their monovalent counterparts as booster doses for persons who are 12 years of age or older in the United States. We previously reported surveillance data from North Carolina on the effectiveness of these two bivalent boosters against coronavirus disease 2019 (Covid-19) during the first 3 months after deployment (September 1 to December 8, 2022); the BA.4–BA.5 subvariants were predominant during the first 2.5 months of this period.1 Here, we present two additional months of data that were obtained during a period when the omicron BQ.1–BQ.1.1 and XBB–XBB.1.5 subvariants had become predominant to show the durability of protection conferred by these two bivalent boosters against a wider range of clinical outcomes than were included in our previous report.

The data sources and study design have been described previously,1-3 and updated information is provided in the Methods section of the Supplementary Appendix, available with the full text of this letter at NEJM.org. The current study used data regarding booster doses and clinical outcomes from September 1, 2022, to February 10, 2023, for all North Carolina residents who were 12 years of age or older. During this period, a total of 6,306,311 residents were eligible to receive bivalent boosters; of these residents, 1,279,802 received the injections. A total of 19,462 of the 154,581 SARS-CoV-2 infections, 253 of the 2208 Covid-19–related hospitalizations, and 79 of the 867 Covid-19–related deaths occurred after receipt of the bivalent booster (Table S1 in the Supplementary Appendix).

We considered four outcome measures: infection, severe infection resulting in hospitalization, severe infection resulting in hospitalization or death, and severe infection resulting in death. We fit the Cox regression model with a time-varying hazard ratio for severe infection and fit the proportional-rates model with a time-varying rate ratio for recurrent infection for each additional booster dose that was received (i.e., first booster vs. primary vaccination, second booster vs. first booster, or third booster vs. second booster); all measures were adjusted for the baseline characteristics shown in Table S1. We estimated the booster effectiveness on a particular day as 1 minus the hazard ratio or rate ratio on that day multiplied by 100%.

Effectiveness of Bivalent Boosters According to the Interval since Administration.

The estimation results are shown in the left column of Figure 1 and in Table S2. Effectiveness against severe infection resulting in hospitalization or death reached a level of 67.4% (95% confidence interval [CI], 46.2 to 80.2) after 2 weeks and decreased to 47.5% (95% CI, 32.6 to 59.2) after 4 weeks, to 44.3% (95% CI, 35.7 to 51.7) after 10 weeks, and to 38.4% (95% CI, 13.4 to 56.1) after 20 weeks. Effectiveness against severe infection resulting in hospitalization was slightly lower, and effectiveness against infection was much lower. The effectiveness against severe infection resulting in death was the highest despite uncertainty because of the small number of events.

We also analyzed the data separately for participants who received bivalent boosters before November 1, 2022 (when the BA.4–BA.5 subvariants were predominant) and after November 1, 2022 (when the BQ.1–BQ.1.1 subvariants were more prevalent and then were gradually replaced by the XBB–XBB.1.5 subvariants). The results are shown in the right column of Figure 1 and in Tables S3 and S4. The effectiveness was broadly similar between the two booster cohorts.

Finally, we performed subgroup analyses according to the participant's age and previous infection status and according to the manufacturers of the bivalent vaccine and the previous vaccine. Effectiveness against infection was higher for the Moderna bivalent vaccine than for the Pfizer–BioNTech bivalent vaccine and higher among previously infected participants than among those with no previous infection .

The two types of bivalent boosters were associated with an additional reduction in the incidence of omicron infection among participants who had previously been vaccinated or boosted. Although the two bivalent vaccines were designed to target the BA.4–BA.5 subvariants, they were also associated with a lower risk of infection or severe infection with the BQ.1–BQ.1.1 and XBB–XBB.1.5 subvariants. The effectiveness was higher against hospitalization and death than against infection and waned gradually from its peak over time.