NIH NATIONAL CANCER INSTITUTE

Frederick National Laboratory for Cancer Research

SERONEWS

Clinical and Translational Serology Highlights

November 2022

Boost Your Chances of Avoiding a COVID Wave

Despite the desire to put the SARS-CoV-2 pandemic in our rearview mirrors for good, subvariants of the virus are likely to remain in circulation for the foreseeable future. This prediction leaves scientists and health care professionals arguing all the more urgently for Americans to receive their COVID-19 booster shots, especially with the onset of fall and winter when more people will be spending time indoors.

The U.S. Food and Drug Administration has granted Emergency Use Authorization (EUA) for bivalent boosters that strengthen immunity against the original SARS-CoV-2 strain and Omicron subvariants BA.4 and BA.5.

Omicron BA.5 transmission grew to dominate U.S. COVID-19 infections this year, peaking mid-summer before beginning to lose ground against a mix of other subvariants in August.

The United States has purchased 170 million doses of the Moderna single-dose bivalent booster (for ages 18 and older) and the Pfizer single-dose bivalent booster (for ages 12 and older). The vaccinations are free and widely available from retail pharmacies such as CVS, Walgreens, Walmart, and others, as well as from many states' and counties' health departments.

Boost Your Chances continues on next page.

Boost Your Chances of Avoiding a COVID Wave (cont.)

Eligible patients can receive either the Moderna or Pfizer bivalent booster regardless of which vaccinations or boosters they previously received for protection against the original SARS-CoV-2 strain and its ensuing Omicron variants. The inoculations can be given two months after primary or booster shots.

Recent results released from Pfizer and BioNTech revealed that a booster dose of their bivalent vaccine induces antibody responses against Omicron BA.4 and BA.5 that are three- to four-fold higher compared to the original version. Moderna has recently revealed that its bivalent vaccine elicits a higher response against Omicron BA.1 than the original strain, with neutralizing protection also detected against the BA.4 and BA.5 strains.

People accustomed to getting their annual flu shot in the fall can add the COVID-19 booster to their routine, since studies indicate that it's safe to get both a COVID-19 vaccine and a flu vaccine at the same time. Combining the two shots may result in a slightly higher chance of side effects such as fatigue, headache, and muscle ache, but the Centers for Disease Control and Prevention reports these symptoms are generally mild and don't last long.

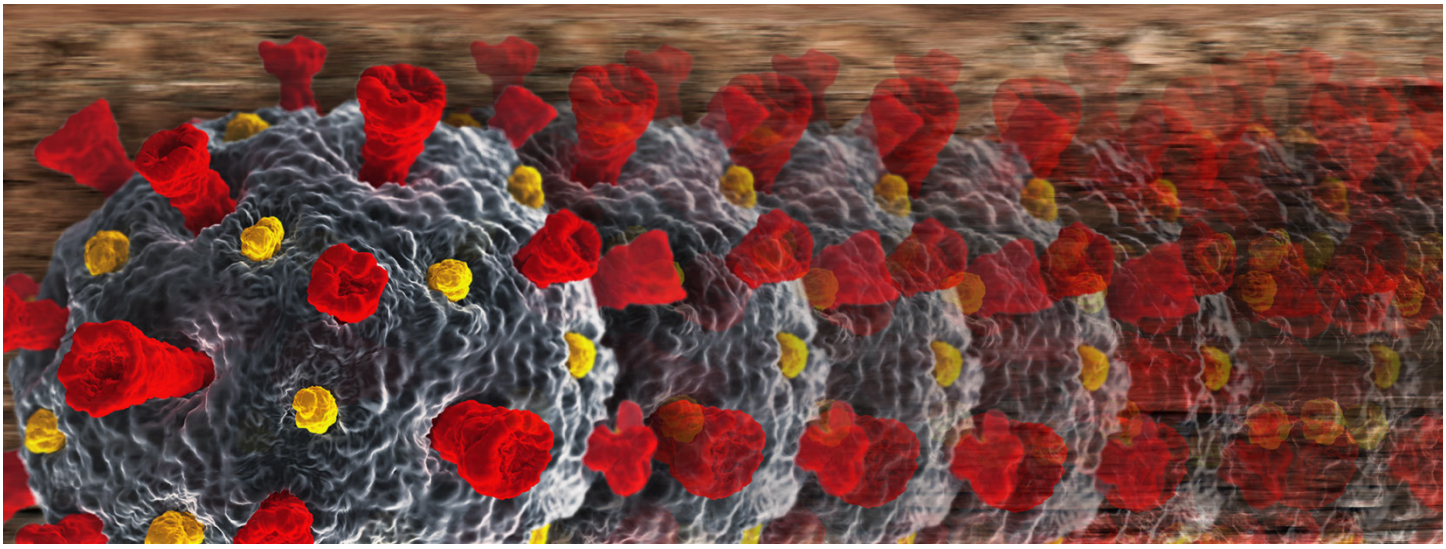
Doctors argue that mild flu-like symptoms are a small trade-off given that, upon infection with COVID-19, the risk of developing severe symptoms that require hospitalization can increase dramatically for the unvaccinated or under-vaccinated. Many infectious disease experts believe that waning immunity from the initial vaccines and the resumption of pre-pandemic socialization patterns mean that those who put off getting their boosters could be facing serious health risks.

This is especially relevant since the Omicron variant continues to mutate into different subvariants that could quickly become a new dominant strain. In a recent interview with CNBC, Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, said that with the onset of the fall and winter months, Americans "shouldn't be surprised" if a new, perhaps more transmissible subvariant begins to make headlines. Because new strains of SARS-CoV-2 have demonstrated an ability to evade existing immunity, there is even greater urgency to get the bivalent booster now since immunization remains the best way to avoid severe illness.

Although the bivalent COVID-19 vaccines received EUA, this doesn't mean they've been approved or licensed by the FDA. While the boosters have been demonstrated to be safe, continued studies, including those by Frederick National Laboratory's Vaccine, Immunity, and Cancer Directorate; NCI; and members of the SeroNet community, are underway to address questions related to their ability to stimulate the immune system.

The Long COVID Road Ahead

Costs of SARS-CoV-2 Infection Coming to Light



Hospitalizations and deaths from COVID-19 are declining in many areas of the world due to vaccination programs and natural immunity gained from recovering from the illness, but serious, ongoing consequences are still being felt by many who have been infected by SARS-CoV-2.

People who experience acute COVID-19 infection, whether mild or severe, can develop a condition commonly called post-acute sequelae of COVID-19 (PASC), or just Long COVID. These people describe a multitude of debilitating symptoms that last three months or longer—in some cases, a year or more—after their initial SARS-CoV-2 infection.

Many of these symptoms have been linked to Long COVID, the most common being shortness of breath, extreme fatigue, and cognitive impairment (also known as "brain fog").

Long COVID continues on next page.

The Long COVID Road Ahead (cont.)

The Centers for Disease Control and Prevention reports that more than 40% of adults in the U.S. reported having COVID-19 since the beginning of the pandemic, and nearly 1 in 5 of those still have symptoms of Long COVID. Recent data from the United Kingdom estimate that Long COVID symptoms are afflicting 2.3 million of its residents (3.5% of the population).

On top of the human cost in suffering and mortality from Long COVID, the U.S. Census Bureau estimates that as many as 4 million people in the U.S. alone can't work due to their Long COVID symptoms, resulting in billions in lost earnings and productivity annually.

These scenarios represent an emerging global crisis.

Assessing a Complicated Disease

One study of more than 13 million health records suggests that vaccination slightly reduces the risk of developing Long COVID, by 15%, though other studies revealed somewhat higher reductions.

Understandably, it's a complex matter. Research suggests that Long COVID may not be one disease with a single cause or mechanism.

One possibility is that the SARS-CoV-2 infection stimulates the immune system to trigger a long-lasting inflammatory response that attacks multiple organ systems. This

Research suggests that Long COVID may not be one disease with a single cause or mechanism.

inflammatory response could be due to the persistence of SARS-CoV-2 or viral particles in the body. COVID-19–induced inflammation may also be linked to reactivation of latent Epstein-Barr virus (EBV) in some Long COVID patients, indicating that some Long COVID symptoms may not be directly caused by SARS-CoV-2.

Another possibility is that SARS-CoV-2 infection triggers an autoimmune response. Autoantibodies have been found in the blood of Long COVID patients suffering from fatigue and shortness of breath, as well as labored breathing and a chronic cough.

Other studies have connected blood vessel microclots and nerve cell dysregulation to Long COVID. Still others suggest that Long COVID triggers the development or exacerbation of other diseases such as diabetes and kidney disease.

Hunting for Markers

With so many ways for Long COVID to manifest, identification of markers that can serve as diagnostic tools and targets for treatment intervention is urgently needed. This research is still in early stages.

One Long COVID immune profiling project revealed not only a marked increase in specific white blood cells normally involved in inflammation and antiviral responses, which can indicate abnormal chronic immune activity, but also that people with Long COVID have approximately 50% less cortisol in their systems than normal.

Elevated levels of specific cytokines, detectable before some Long COVID patients develop their symptoms, may help in the future to

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predict disease risk and let doctors know ahead of time that those patients are susceptible.

Other studies are aiming to identify blood biomarkers related to Long-COVID-associated vascular problems.

Having type 2 diabetes, or the presence of SARS-CoV-2 or EBV, or specific autoantibodies, in the bloodstream at the time of the initial COVID-19 diagnosis are risk factors that appear to correlate with the development of Long COVID.

Supporting Patients, Searching for Cures

Meanwhile, large-scale efforts to address Long COVID have begun.

The U.S. has created the National Research Action Plan on Long COVID, which introduces the first government-wide national research agenda focused on advancing prevention, diagnosis, treatment, and provision of services and support for people affected by Long COVID.

With it is the U.S. Services and Supports for Longer-Term Impacts of COVID-19 report. It outlines federal services available to the public for Long COVID and related conditions, as well as other impacts on individuals and families. It provides information resources for both patients and health care personnel, including services for individuals confronting challenges related to mental health, substance use, and bereavement.

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COVID. Several efforts are underway in the U.S. and abroad.

The National Institutes of Health is bringing together scientists, clinicians, patients, caregivers, and community leaders, collectively called the RECOVER Consortium, to determine how to prevent, treat, and recover from Long COVID.

The National Institute of Health Research in the United Kingdom has assembled and funded the LOCOMOTION–Long COVID Study to treat and support Long COVID patients in the UK. This study encompasses 10 clinical sites devoted to developing guidelines of care for patients, determining symptom triggers to aid in self-management, and monitoring care clinic results to improve health care.

Non-government agencies are also conducting privately funded studies. The Long COVID Research Initiative, based at the nonprofit PolyBio Research Foundation in Washington state, was launched in response to the efforts of several patient advocates who were dealing with Long COVID. The first focus will be on research to determine whether SARS-CoV-2 persists in Long COVID patients and is responsible for their symptoms. If the virus is found to be lingering

Long COVID continues on next page.

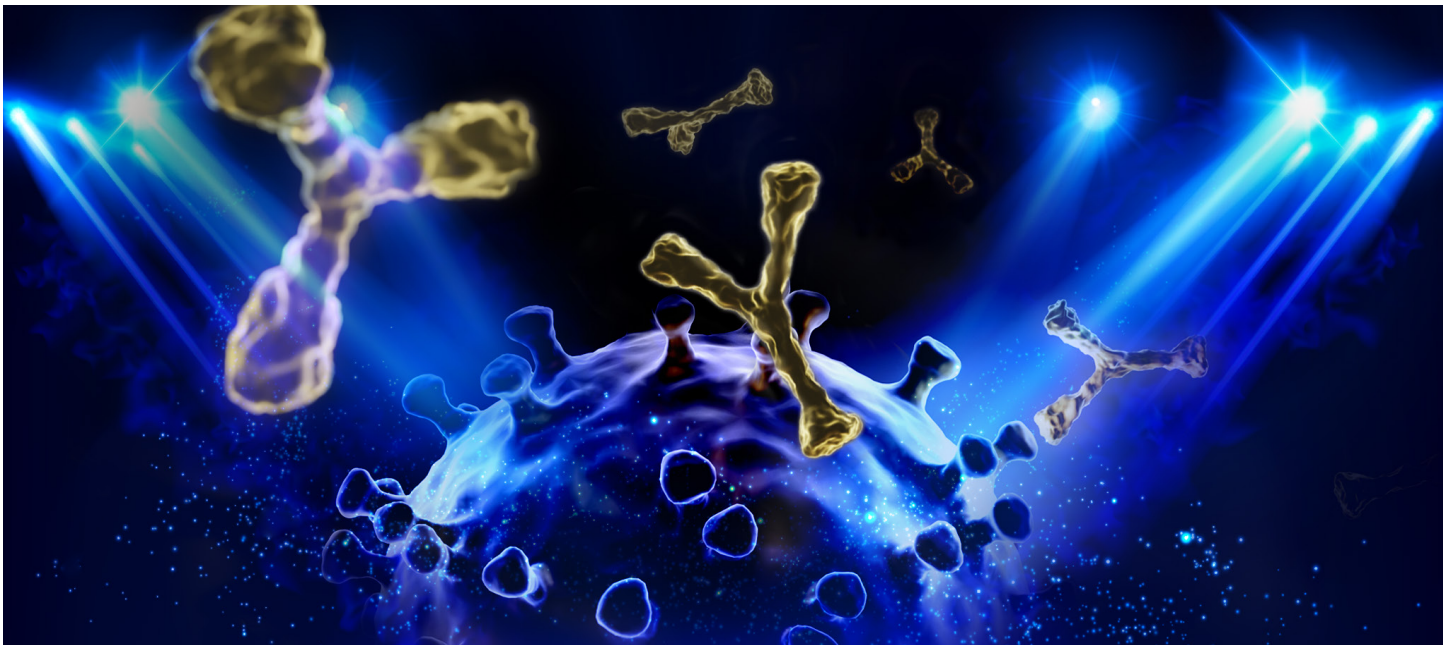
The Long COVID Road Ahead (cont.)

in patients' bodies, the hope is that antiviral treatment could address the symptoms.

In the meantime, people with Long COVID are trying to cope with a "new normal" and worrying about their futures. The Omicron variant continues to spawn subvariants that break through both natural and vaccine-induced immunity, threatening to upend even more lives with Long COVID. It will be vital to maintain momentum in the search for Long COVID treatments and prevention methods as the world adjusts to living with COVID-19.

Neutralizing Antibodies Move to Center Stage

Optimal Neutralization Key to Vaccinating Against Emerging SARS-CoV-2 Variants



Nearly three years into the COVID-19 pandemic, SARS-CoV-2 has shown itself to be a challenging adversary.

Despite the advent of effective vaccines, SARS-CoV-2 continues to infect and reinfect in waves worldwide, in part due to rapid mutations in its spike protein, the part that antibodies elicited by current vaccines are designed to recognize and bind.

These mutations have been the major factor in the Omicron variant's global spread and dominance over the past year. The 2022 COVID-19 surge caused by Omicron subvariant BA.5, which was responsible for the majority of U.S. cases by August, is now waning, but Omicron subvariant BA.4.6 and BA.5 offshoot subvariants, such as BQ.1 and BA.2.75, have moved into the picture, and their infection rates are starting to climb.

Measuring Neutralizing Antibody Protection

Viral mutations permit new SARS-CoV-2 variants to evade the immune response and infect people who were vaccinated against a previous strain of the virus or who have natural immunity after recovering from COVID-19, causing breakthrough infections. Protection resulting from vaccination and previous infection alike is believed to be mediated by neutralizing antibody responses.

But as SARS-CoV-2 changes, existing antibodies that bind the virus may no longer actually neutralize the variant, and thus not confer effective immunity.

Consequently, measurements obtained from binding assays such as ELISAs, which measure total antibodies regardless of neutralizing activity, may not fully reflect protection against the latest variants.

That makes measuring and understanding neutralization especially important as new variants of interest continue to emerge.

Assaying people's samples, such as serum from blood, for neutralizing antibodies is an accurate method, but neutralization assays are time-consuming, labor intensive, expensive, and much more variable compared to binding ELISAs. The conventional virus neutralization test, the gold standard for detecting neutralizing antibodies, requires a biosafety level 3 laboratory and isn't amenable to high-throughput screening techniques that quickly test large volumes of samples in clinical studies.

Neutralizing Antibodies continues on next page.

Neutralizing Antibodies Move to Center Stage (cont.)

Other options exist, however. Pseudovirus-based virus neutralization tests for SARS-CoV-2 are higher-throughput and can be used in a biosafety level 2 laboratory, though they are still cell-based and share a lot of the same limitations as conventional neutralization assays. Another option is the surrogate virus neutralization test, which detects neutralizing antibodies without the need for live virus or cells. There are currently two surrogate SARS-CoV-2 neutralization assays approved under Emergency Use Authorization by the Food and Drug Administration.

Understanding neutralizing antibodies is also crucial for defining a possible correlate of protection for SARS-CoV-2—a specific immunological benchmark of whether someone is guarded against infection—which is a work in progress. This requires comparing large immunological datasets from different clinical trials using validated assays, but this has been difficult because of differences in assays, target antigens, numerical readouts, and endpoints.

The variability found in neutralization assays could be minimized if testing facilities would validate their assays and express neutralization titers in international units in their publications and the data they submit to their regulatory authorities. Similarly, they could standardize their results against the World Health Organization International Standard (WHO IS) for anti-SARS-CoV-2 immunoglobulin, which is validated for use in neutralizing antibody assays, or the U.S. Serology Standard if the WHO IS is not available.

> ***... the hope is that mucosal vaccines will elicit local immune responses ...***

Mucosal Neutralization

And the task isn't limited to serum tests. Mucosal neutralizing antibody serology testing is going to gain importance as mucosal vaccines—those administered through a mucous membrane, like the nostrils or mouth—make their way into the vaccine toolkit. Researchers will need to determine whether these vaccines are as effective at inducing protective immunity as systemic vaccines.

In India, the world's first preventive, mucosal vaccine against COVID-19 was recently approved for emergency use in adults as a primary vaccine in the form of nose drops. In China, teams are using a nebulizer to turn the currently available liquid vaccine into an inhalable mist, which is approved for use as a booster. Both vaccines use harmless adenoviruses as vectors to deliver the SARS-CoV-2 genetic material into the host cells.

Since mucosal surfaces are where SARS-CoV-2 gains entry to cause COVID-19, the hope is that mucosal vaccines will elicit local immune responses that offer better protection at the sites of infection than the intramuscularly injected vaccines, preventing SARS-CoV-2 from taking hold in a person and being transmitted to others.

No matter how the vaccine is administered, or which detection assay, sample, or lab is used, being able to accurately quantify and compare levels of neutralizing antibodies against SARS-CoV-2 is going to be key to developing the most effective strategies for protection against COVID-19 in our quest to manage this disease and end the pandemic.

Past Events

Monthly Meetings

Tues, 7.12.22

Immunogenicity of COVID-19 Vaccine Boosting in Nursing Home Residents
Dr. David Canaday, Case Western Reserve University

Vaccine-induced Antibody Magnitude, Breadth, Durability, and Correlates of Immunity: Insights from the Prospective Assessment of SARS-CoV-2 Seroconversion (PASS) Study
Dr. Edward Mitre, Uniformed Services University

Tues, 9.13.22

Federal Efforts to Address the Longer-Term Impacts of COVID-19
Dr. Deborah Porterfield, U.S. Department of Health and Human Services

Burden, Prevalence, and Trends of Long-Term Sequelae of SARS-CoV-2
Dr. Sharon Saydah, Centers for Disease Control and Prevention

Tues, 10.11.22

COVID-19 mRNA Vaccine Anaphylaxis: Experience from a Double-Blinded Cross-Over Clinical Trial (COVAAR)
Dr. Pamela Guerrerio, National Institutes of Health, National Institute of Allergy and Infectious Disease

CDC's COVID-19 Vaccine Safety Monitoring and Data on Anaphylaxis
Dr. Margaret Cortese, Centers for Disease Control and Prevention

Past Events

Monthly Meetings (cont.)

Tues, 11.8.22

Rapid and Scalable Self-Testing for SARS-CoV-2 Antibodies: Approach, Findings and Potential of the REACT-2 Study Model
Dr. Helen Ward, Imperial College London

Update on SARS-CoV-2 Variants and the Epidemiology of COVID-19
Dr. Heather Scobie, Centers for Disease Control and Prevention

Precision Surveillance of SARS-CoV-2 Variants in the Mount Sinai Health System
Dr. Honoratus Van Bakel, Icahn School of Medicine at Mount Sinai

Focus Group Meetings

All Focus Group Meetings have been/are being cancelled through the end of 2022.

Round Table Meetings

Mon, 8.22.22

Topic: ***Neutralization Assays: Where Are We Now?***

Duke COVID-19 Vaccine Laboratory Program for Neutralizing Antibody Assays
Dr. David C. Montefiori, Duke University of School of Medicine

An In Vitro Microneutralization Assay for SARS-CoV-2 Serology
Johnstone Tcheou, Icahn School of Medicine at Mount Sinai

Evaluation of COVID Therapeutic Antibody Products
Dr. Michael Holbrook, NIAID Integrated Research Facility

Correlates of Neutralization Activity for Manufacture of COVID-19 Convalescent Plasma
Dr. Carlos Villa, CBER/U.S. Food and Drug Administration

Mon, 10.24.22

Topic: ***Evaluation of Mucosal Immune Responses to SARS-CoV-2 Infection and Vaccines: Key Methodological Mucosal Sampling and Testing Considerations***

Nasal Swabbing and Analysis of IgA Antibodies in Secretions from Humans and NHP
Dr. Pamela Kozlowski, Louisiana State University Health Sciences Center New Orleans

Methodological Considerations for Measurement of Mucosal Humoral Immune Responses to SARS-CoV-2
Dr. Chris Heaney, Johns Hopkins University

Overview of NIAID's Mucosal Sampling Study (DMID 21-0012 "MixNMatch" Cohort 2) and IDCRC's Adaptive Mucosal Vaccine Protocol
Dr. Chris Roberts, National Institute of Allergy and Infectious Diseases

Upcoming Events

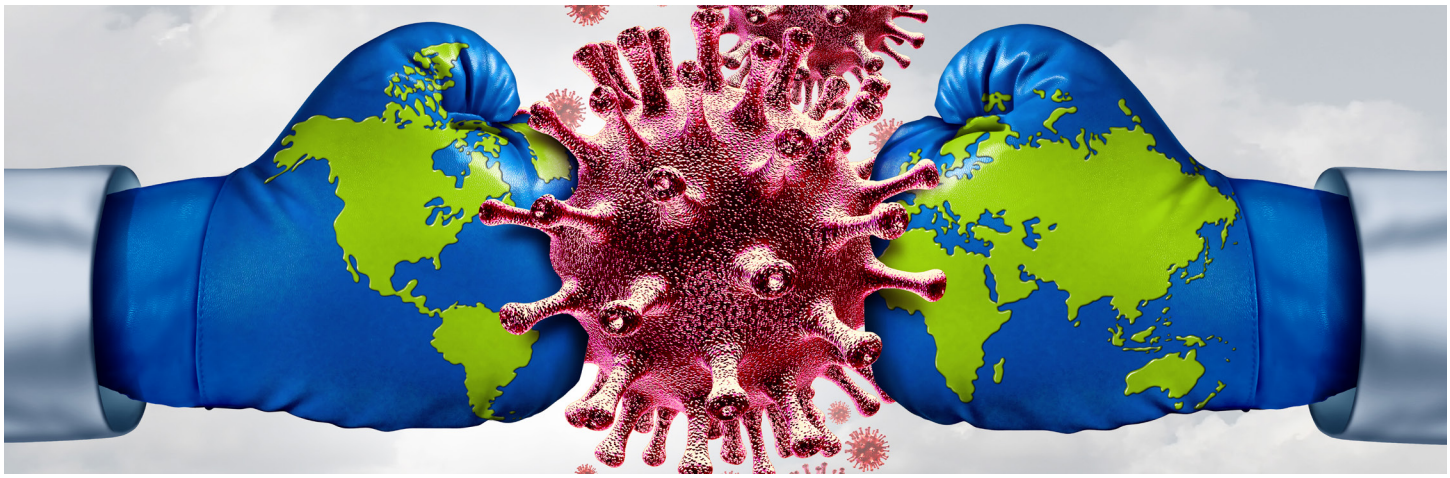
Monthly Meeting: Tuesday, December 13, 2022

Focus Group Meeting: Friday, January 20, 2023

Round Table Meeting: Monday, February 27, 2023

COVID Is Still a Global Public Health Threat

Bivalent Vaccine Can Boost the Odds of Preventing the Next Surge



The Clinical and Translational Serology Task Force had a busy summer schedule, bringing together stakeholders from academia, industry, and government to present and discuss the latest research findings and technological advancements in the areas of COVID-19 vaccines and neutralization assays, as well as to hear about programs aiming to help those who are battling Long COVID.

The COVID-19 pandemic outlook is much better than it was one or two years ago. However, about 2,500 individuals in the U.S. are still dying from COVID-19 every week, and the virus is still rapidly mutating and spreading. Although it is unclear when the next surge will happen, for the past two years COVID-19 cases have risen during the fall and winter months. Lifting of mask mandates, waning immunity from prior infections, and very low vaccination rates with the new bivalent booster shots raise worries about the course of the pandemic as we head into the holiday season. Results from the bivalent vaccine seem promising so far, suggesting that getting a COVID-19 bivalent booster will provide protection against the circulating Omicron strains. With these new tools there is a greater chance of preventing the next wave of SARS-CoV-2 infections and severe COVID-19 disease.

We look forward to continued engagement and discussion as we all move through the evolving challenges of this pandemic. We welcome your suggestions, comments, and requests, and we're looking forward to working with and hearing from all of you.

Safe and Happy Holidays!

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