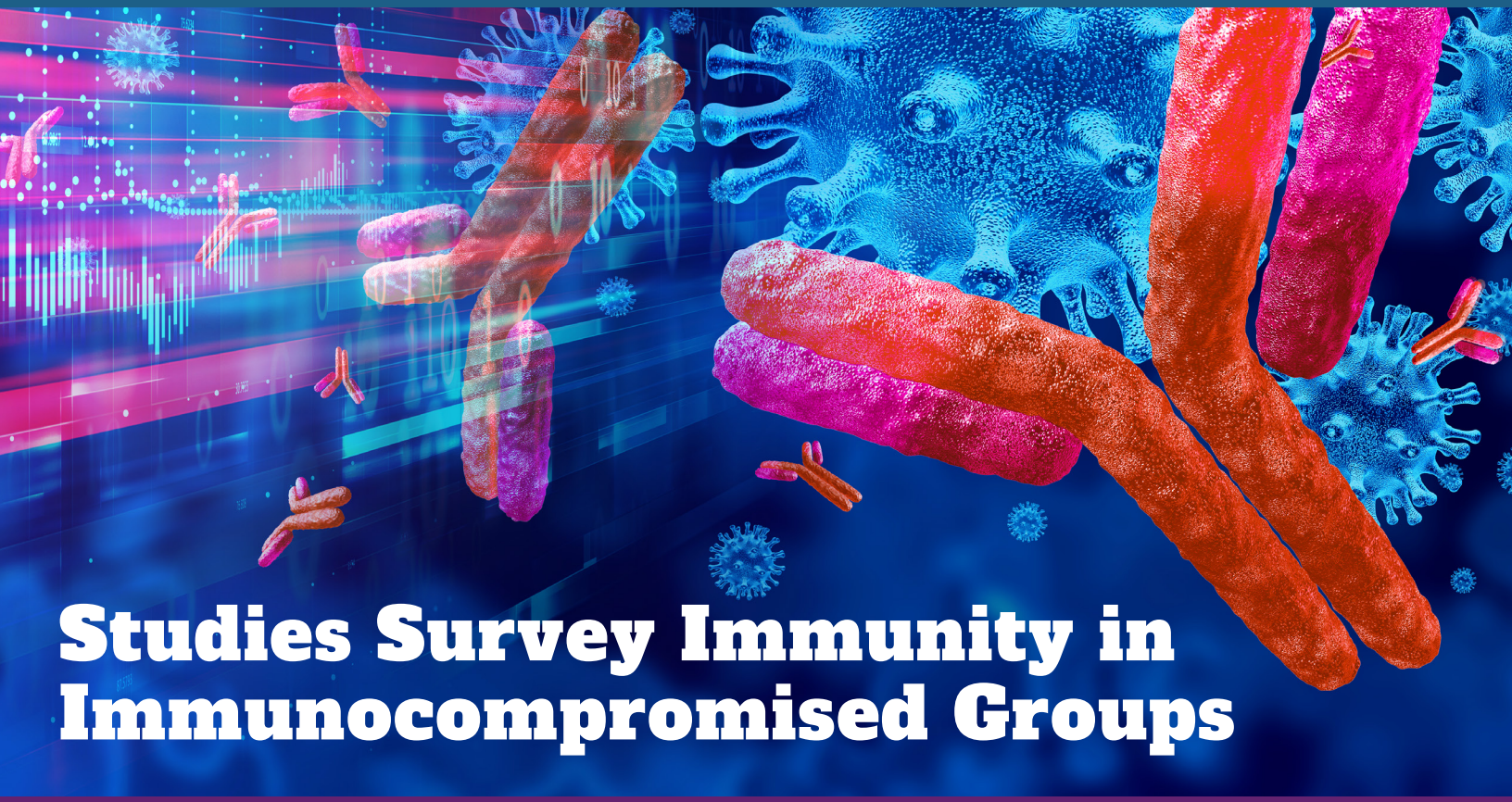
NIH NATIONAL CANCER INSTITUTE

Frederick National Laboratory for Cancer Research

SERONEWS

Clinical and Translational Serology Highlights

July 2022



Studies Survey Immunity in Immunocompromised Groups

Research is revealing a clearer picture of vaccination, immunity, and COVID-19 in cancer patients and other immunocompromised people.

Since the early phases of the pandemic, scientists and physicians have known these individuals are especially vulnerable to severe disease, complications, and death from COVID-19. However, their immune system responses to SARS-CoV-2 vaccines were unclear, as initial vaccine trials did not include cancer patients.

The data have since accumulated, illustrating varied responses that tend to be lower than people with unaffected immune systems. Patients with cancer, particularly those with blood cancers, are at increased risk of COVID-19. Blood cancers often cause alterations in immune cells that produce antibodies against the virus.

The Centers for Disease Control and Prevention recommends that moderately to severely immunocompromised adolescents and adults receive three mRNA vaccine doses and a booster. Children should receive three doses.

Studies Survey Immunity continues on next page.

Studies Survey Immunity (cont.)

The National Cancer Institute is conducting a study in nearly 1,800 cancer patients who had COVID-19 to learn more about risk factors and help doctors better manage treatment for similar patients. Meanwhile, the COVID-19 and Cancer Consortium, a partnership between nearly 130 cancer centers and related organizations in North America, is compiling large quantities of serological and clinical information on cancer patients who have been diagnosed with COVID-19.

Another study, led by consortium members at Dana-Farber Cancer Institute, analyzed breakthrough infections in cancer patients vaccinated against SARS-CoV-2. Fully vaccinated patients who suffered a breakthrough infection had hospitalization and mortality rates comparable to unvaccinated patients. Vaccinated patients with blood cancers were a disproportionately large part of those cases, underscoring that patients' immune responses to vaccines depend on their type of cancer.

The team stressed the importance of such patients taking additional protective measures, like booster vaccination, masks, and physical distancing.

In a separate study unconnected to the consortium, a team from Moffitt Cancer Center examined antibody titers before and after vaccination in 515 cancer patients who received the Moderna mRNA-1273 vaccine. After the first dose, 71.3% of cancer patients had developed antibodies. This level rose to 90.3% after the second dose.

However, antibody responses were vastly different between cancers. Just 49.1% of patients with lymphoid cancers manifested detectable antibodies—the lowest rate among the participants—with some lymphoid cancer subgroups having still lower response rates.

Certain types of cancer treatment, especially BTK inhibitors and anti-CD20 antibodies, correlated with poor antibody response. Only 33% of patients receiving BTK inhibitors had detectable antibodies after two doses. Among vaccinees who had received anti-CD20 antibodies within six months before vaccination, a mere 6.3% manifested SARS-CoV-2 antibodies.

The study also quantified the patients' antibody levels, which varied widely depending on the type of cancer and treatment.

While the precise threshold of antibody levels needed to provide protection from SARS-CoV-2 remains unknown, comparative data allow scientists to contextualize immune responses in immunocompromised patients versus responses believed to offer some degree of protection in healthy populations. That information can guide medical decisions on boosters for immunocompromised groups.

Scientists from the Icahn School of Medicine at Mount Sinai and SeroNet took a similar tack by investigating antibody responses to booster vaccination (a third mRNA vaccine dose) in 476 patients with multiple myeloma, a blood cancer. The booster elicited detectable antibody levels in 88% of patients who had detectable antibodies after the standard two-dose mRNA vaccine regimen. It also increased recipients' antibody levels.

The team concluded that these cancer patients should receive a booster yet acknowledged the patients' antibody levels remained substantially lower than those in healthy controls, in some cases as low as 100-fold. That underscores the need for physicians to monitor such patients for the possible need of additional doses thereafter, the team posited.

As studies continue to improve our understanding of immunity to COVID-19, data like these have the potential to guide further policy on booster schedules and preventive measures for immunocompromised groups. That remains crucial for an exit to the pandemic for all people.

Tale of Two Immunities

Research compares vaccination and past infection.

Among efforts to better understand immunity against COVID-19, much attention has centered on vaccination, but understanding immunity after infection is equally important. Scientists are filling gaps in COVID-19 immunology knowledge and gaining greater insight into controlling the virus by studying both scenarios.

Recovery from an infection with SARS-CoV-2 can confer some protection against future, repeat infection. Laboratories are characterizing immune responses, and the durability

Tale of Two Immunities (cont.)

of those responses, in unvaccinated people who were previously infected with the virus, including learning how protection gained from infection compares to protection gained from vaccination.

Knowledge of SARS-CoV-2 and vaccine immunology will continue to evolve, especially as new variants emerge. This wider view can reveal how different aspects of the immune system interact with the virus under different conditions—and, potentially, highlight key factors that may influence protection against COVID-19.

Infection Induces Potent Responses in Some

Both natural infection and vaccination elicit an antibody response in most people, but protection isn't as simple as having antibodies. They must be potent enough to neutralize the circulating viral strains and numerous enough to put up a real fight.

Several studies and retrospective analyses have so far shown that the antibodies maintain their potency and remain at effective levels for several months after either infection or vaccination. In October 2021, the Centers for Disease Control and Prevention (CDC) noted that antibodies generated through both infection and vaccination were able to neutralize different SARS-CoV-2 variants, although the data predated the emergence of the Omicron variant.

Yet differences have emerged between vaccination- and infection-induced immunity. Some studies have indicated that protection against SARS-CoV-2 isn't always equivalent between the two.

Data suggest that people who recover from COVID-19 have decreased risk of future infection from SARS-CoV-2 variants that are similar to the strain that previously infected them. Antibodies from previously infected people also retained partial efficacy against the Omicron variant a year after the individuals' first, non-Omicron infection in one study.

Meanwhile, several studies have demonstrated that vaccines designed against the original SARS-CoV-2 strain have lower efficacy against variants that differ substantially from the original strain.

Infection-induced immunity varies considerably from person to person, making it less predictable than vaccination-induced immunity. Vaccination has been shown to induce protective immune responses and significantly reduce the chances of developing COVID-19. The CDC recommends vaccination even in individuals with evidence of a previous infection since vaccination will safely boost immunity gained from previous infections.

One study demonstrated that a single dose of an mRNA vaccine given after recovery from infection substantially decreases a person's chances of reinfection. Other research suggested that this "hybrid immunity" increases the immune system's ability to neutralize variants of concern, including Omicron. Such findings suggest that vaccination not only reliably stimulates immune responses but remains the safest and most predictable way to obtain a more consistent level of protection.

Additional studies and analyses to further illuminate vaccination- and infection-induced immune responses are ongoing.

Opportunity and Obstacles

Amid a global vaccination effort rife with obstacles, the opportunity to do more abounds.

Vaccines offer hope toward ending the global pandemic caused by SARS-CoV-2. Mass vaccination worldwide has made substantial progress but faces persistent challenges, vaccine inequity entrenched among them.

A year into the pandemic, efforts to develop and distribute a vaccine produced several safe and effective options. By now, more than 30 vaccines have been approved for general or emergency use in different parts of the world. Nearly 350 vaccine candidates have been developed or are in development. Of those, almost 130 are in clinical trials.

Opportunity and Obstacles continues on next page.

Opportunity and Obstacles (cont.)

As of June, 65.7% of the world's population has received at least one dose of a COVID-19 vaccine. Affluent nations—especially those in Europe and North America—and nations producing the licensed vaccines have achieved full vaccination in substantial portions of their populations, over 75% in some cases.

But other parts of the world still aren't as far ahead. Among low-income countries, only 16.2% of people have received at least one dose.

The international COVID-19 vaccine landscape is at a threshold, and equity will be key for the next steps.

A Global Vaccination Gap

In many ways, this disparity between high-income and low-income nations is unsurprising. Wealthier countries have robust medical and logistical infrastructure conducive to transporting and storing vaccines, many of which must be kept at specific temperatures that can be hard to maintain without specialized equipment.

Smaller and less affluent countries simply don't have enough of the necessary resources. They also lack the funds to purchase the large quantities of vaccine necessary to immunize their populace. Instead, they must depend largely on donations and consortium efforts, which are still subject to logistical and collaborative limitations and the supply of available, unused vaccines.

For instance, the international COVAX effort has shipped almost 1.5 billion doses to 145 countries: a tremendous achievement but also only a dent in the number of vaccines required for full immunization worldwide.

Although there was a global shortage of COVID-19 vaccines in 2021, the vaccine supply should no longer be a limiting factor to more equitable coverage. Scaling up the manufacturing capacity for currently available vaccines through COVAX and other initiatives can help secure the World Health Organization's target coverage, and the means exist to do so.

It will be critical for the next generation of vaccines to clear other hurdles: logistics, cost, and storage and manufacturing requirements. Vaccination efforts must incorporate safe, effective, and affordable options that can be produced and stored in lower-income and resource-limited settings, including rural and isolated regions.

Among the options are vaccines that require fewer doses, allow longer periods between boosters, and are free from special storage conditions. These would translate to fewer clinical visits for people in impoverished areas, less economic and medical burden, decreased logistical requirements, and improved accessibility.

Multiple Platforms Create Opportunity

Efficacy and safety are still important, too. Next-generation vaccines will need to contend with variants' ability to partially avoid immunity, including antibodies generated by some existing vaccines.

Durability—how long the vaccine remains effective—is also crucial, especially in resource-limited settings where a sustained booster administration program isn't feasible.

Vaccination efforts must incorporate safe, effective, and affordable options...

Manufacturers are pursuing multiple platforms to make effective, durable, and practical vaccine candidates. Among them are mRNA, viral vectors, inactivated and live-attenuated viruses, plasmid DNA, viral protein subunits, and virus-like particles. Each has its own advantages.

Several of the candidates require an adjuvant to stimulate an immune response. While that adds another layer to manufacturing, it can be managed. Adjuvanted vaccines have long been used against other pathogens.

Some of the methods may result in vaccines that drive protection against SARS-CoV-2 for longer periods than the current vaccines. Others could be more effective against variants. The variety of techniques creates many opportunities for better understanding and stimulating robust, long-term protective immune responses in vaccine recipients.

Different platforms carry the added benefit of being easier to manufacture and store, particularly in resource-limited settings, than some currently licensed vaccines. Multiple vaccine candidates in development can be produced using existing local infrastructure in some developing and less-developed countries.

Major efforts are also underway to increase manufacturing capacity and improve planning in underequipped regions to better meet global needs during pandemic threats.

Overcoming Hesitancy

Having a variety of platforms may help address vaccine hesitancy, another important barrier encountered in immunization efforts.

Misgivings and concerns about vaccination have been identified globally. The U.S., for instance, has vaccinated 66.3% of its population, but Centers for Disease Control and Prevention surveys show vaccine hesitancy in up to 26.7% of respondents in particular regions of the country.

The challenge is compounded by scientific misinformation as well as worries over side effects, novel platforms, and the speed at which the vaccines were developed.

Some of the currently licensed and next-generation vaccines use platforms that mirror or resemble those of other widely used and trusted vaccines, like the one for influenza. There's hope among the scientific community that this knowledge, combined with additional outreach, education, and trust-building efforts, could sway the hesitant.

There isn't a "one size fits all" solution to something as complex as exiting the pandemic. The licensed vaccines have given the world options, and the next-generation candidates in development hold the potential to give many more. The global community will need to decide to take an equitable path.

Standards Updates

U.S. SARS-CoV-2 Serology Standard

Entity	U.S. Standard Requests	Evaluation Panel Requests
Pharma/Biotech	65	4
U.S. Government	12	2
SeroNet	29	12
Academic	40	1
Other	8	0
TOTAL	154	19

The U.S. SARS-CoV-2 Serology Standard, a tool to enable serology assay harmonization and to increase comparability of results from different serology studies, continues to be distributed to a growing number of users.

The U.S. standard is calibrated against the WHO International Standard (IU/mL). Interested parties within the scientific community can request the U.S. standard via the downloadable request form on the Frederick National Laboratory website.

WHO Manual

The Expert Committee on Biological Standardization has recommended the adoption of the *WHO manual for the establishment of national and other secondary standards for antibodies against infectious agents focusing on SARS-CoV-2*.

A copy of the draft version is available online.

Past Events

Monthly Meetings

Tues, 2.8.22

Immunogenicity of SARS-CoV-2 mRNA 1273 Vaccination Among Cancer Patients
Dr. Anna Giuliano, Professor and Director, Center for Immunization and Infection Research in Cancer; American Cancer Society Clinical Research Professor

COVID-19 in Patients with Cancer: Specific Considerations in a Vulnerable Population
Dr. Ziad El Bakouny and **Dr. Chris Labaki**, Dana-Farber Cancer Institute

Tues, 3.8.22

Safety, Immunogenicity, and Efficacy of NVX CoV2373 in Adults and Adolescents
Dr. Karen Kotloff, Professor, University of Maryland School of Medicine

Development of a Newcastle Disease Virus-based COVID-19 Vaccine
Dr. Florian Krammer, Professor, Icahn School of Medicine at Mount Sinai

Tues, 4.12.22

Real-World Data in the COVID Era: The Role of SARS-CoV-2 Serology
Dr. James Crawford, Professor and Chair, Department of Pathology and Laboratory, Medicine Donald and Barbara Zucker School of Medicine at Hofstra/Northwell; Senior Vice President of Laboratory Services, Northwell Health

Duration of Protection Against SARS-CoV-2 Reinfection and Associated Risk of Reinfection Assessed with Real-World Data
Dr. Shannon Reynolds, Vice President, Science, Aetion

Tues, 5.10.22

CORBEVAX: Recombinant Protein COVID-19 Vaccine for Global Health
Dr. Peter Hotez, Baylor College of Medicine

Global Vaccine Equity: Evolving the Global Strategy to Match the Science
Dr. Krishna Udayakumar and **Dr. Gavin Yamey**, Duke Global Health Institute

Tues, 6.14.22

The HARMONY Study: Towards a Greater Comparability Between SARS-CoV-2 Binding Antibody Assays
Dr. Amanda Semper, Public Health England; **Dr. Mark Page**, National Institute for Biological Standards and Control

Serology Assay Comparison Study (SACS): Summary
Dr. Troy Kemp, Frederick National Laboratory for Cancer Research

Focus Group Meetings

Fri, 2.18.22

Development of STI-9199, a Broadly-Acting SARS-CoV-2 Neutralizing mAb for Intranasal Administration
Dr. Robert Allen, Senior Vice President R&D, Sorrento Therapeutics

New mRNA Vaccine Developments Against Omicron and the Next Variants
Dr. Randall Hyer, SVP, Global Medical Affairs, Moderna

Fri, 3.18.22

Serum Antibody Testing as Diagnostic Criteria for COVID-19 Cases with Negative Nucleic Acid Tests in China
Dr. Yang Xu, Director, Laboratory of Special Diagnosis, Shanghai University of Medicine and Health Sciences

Allocetra™: Off-the-Shelf, Universal, Macrophage Reprogramming Cell Therapy for Life-Threatening Diseases; COVID-19, Sepsis, Hemorrhagic Shock; Multi-organ Failure and Other Conditions
Dr. Dror Mevorach, CSO, Enlivex; Director, Rheumatology Research Center and Molecular Immunology; and Director, Centre for Rare Diseases, Hadassah Medical Center, Jerusalem

Fri, 5.20.22

Does SARS-CoV-2 Carry the Hallmarks of an Oncogenic Virus? Next Generation Innate and Adaptive Cell Mediated Vaccines & Therapies to Prevent and Treat Virally Induced Cancers
Dr. Patrick Soon-Shiong, ImmunityBio, NantHealth

FDA's Efforts to Facilitate COVID-19 Vaccine Development and Availability
Dr. Peter Marks, U.S. Food & Drug Administration

Round Table Meetings

Mon, 2.28.22

Topic: ***Protective Immunity from Infection and Vaccination: What Is the Evidence from Large Studies?***

Immunity Following SARS-CoV-2 Infection and COVID-19 Vaccination: Lessons Learned and Remaining Gaps
Dr. Melissa Briggs-Haggen, Applied Epidemiologic Studies Team Lead, RVB, DVD, NCIRD, Centers for Disease Control and Prevention

Protection of Natural Immunity and Vaccine Immunity: Findings of Two Years of COVID-19 Epidemiology Research in Qatar
Dr. Laith Jamal Abu-Raddad, Professor of Population Health Sciences, Weill Cornell Medical College

Effectiveness of BNT162b2 Vaccine after Recovery from COVID-19
Dr. Ronen Arbel, Health Outcome Researchers, Clalit Health Services

Mon, 4.25.22

Topic: ***Role of T Cells in Protection against COVID-19: From Knowledge to Clinical Practice***

Adaptive Immune Dysregulation in Cancer Patients During SARS-CoV-2 Infection and Vaccination
Dr. Santosha Vardhana, Memorial Sloan Kettering Cancer Center

Challenges in Measuring T-Cell Responses Discussed on the Basis of a Phase 1 Study of an MVA-based COVID-19 Vaccine Candidate
Dr. Christine Dahlke, University Medical Center Hamburg-Eppendorf

Assessment of the SARS-CoV-2 Specific T-Cell Response – The Hamburg Experience
Dr. Julian Schulze zur Wiesch, University Medical Center Hamburg-Eppendorf

A Molecular Dx for Assessing the T-Cell Response to SARS-CoV-2
Dr. Harlan Robins, Adaptive Biotechnologies

Mon, 6.27.22

Topic: ***Understanding the Role of SARS-CoV-2 Serology Using Real-World Data: Where are we now? Where do we want to be? How do we get there?***

SARS-CoV-2 Antibody Testing in Current Clinical Infectious Disease Practice: Results of a CDC-IDSA Survey of Infectious Disease Physicians in the U.S., March 2022
Dr. Adi Gundlapalli, Centers for Disease Control and Prevention

FDA's Real-World Evidence Program
Dr. Kenneth Quinto, U.S. Food and Drug Administration

SARS-CoV-2 Serology: Vulnerability to COVID-19 Infection and Adverse Outcomes
Dr. Nigel Clarke, Quest Diagnostics

A Proposed RWD Infrastructure to Support Understanding of SARS-CoV-2 among Higher Risk Subpopulations
Dr. Lynne Penberthy, National Institutes of Health/National Cancer Institute

Upcoming Events

Round Table Meeting: Monday, August 22, 2022

Monthly Meeting: Tuesday, September 13, 2022

Focus Group Meeting: Friday, September 16, 2022

Leadership Corner

Global Collaboration Remains Critical

Cooperative research efforts yield promising standardization results.

The Clinical and Translational Serology Task Force and the SeroNet community have worked together extensively to respond to the coronavirus pandemic. Continued collaboration is pivotal as SARS-CoV-2 and its latest variants have evolved to be more transmissible and to better evade people's immune responses. The latest Omicron subvariants can infect even those who were previously vaccinated and infected. The Clinical and Translational Serology Task Force continues to encourage broad implementation of serology standardization, and recently completed an assay comparison study involving 28 different assays widely used across the SeroNet community, with very encouraging results. To better leverage the power of large, standardized serology and clinical datasets, real-world data analyses are being pursued to address key questions regarding protection against Omicron and its subvariants following infection and vaccination, as well as to better understand the role of boosters.

We welcome your suggestions, comments, and requests, and we're looking forward to working with and hearing from all of you.

We look forward to your feedback and wish you all the best.

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SeroNews is produced by the Scientific Publications, Graphics & Media department at the Frederick National Laboratory for Cancer Research and published by the National Cancer Institute and the Frederick National Laboratory. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. government.

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The SeroNet Initiative is funded by the National Cancer Institute (NCI) under contract number 75N91019D00024.