UCSF Institute for Global Health Sciences

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COVID-19 Research Watch
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BIOENGINEERING

Design of SARS-CoV-2 hFc-Conjugated Receptor-Binding Domain mRNA Vaccine Delivered via Lipid Nanoparticles[1]

Elia et al. explore the development of a SARS-CoV-2 mRNA vaccine that is enhanced by lipid nanoparticle (LNP) delivery. The authors focused on the receptor-binding domain (RBD) of SARS-CoV-2 fused to IgG-Fc as the target antigen for the mRNA coding sequence. As demonstrated in clinically available products, the fusion of the IgG-Fc domain to a protein increases half-life, immunogenicity, solubility and delivery efficiency. To determine the LNP formulation with optimal distribution, protein expression, and kinetics, an *in vivo* luciferase mRNA reporter assay was performed. By examining the immune response towards the luciferase protein, two LNP formulations that presented a strong cellular response were chosen to evaluate SARS-CoV-2 RBD-hFc mRNA vaccination (delivered via two-shot regimen, primer and booster 25 days later). An antibody response was detected 14 days after the boost in both LNP-encapsulated mRNA compositions. Incorporating rRBD-hFc led to a boost effect in antispike antibody titer and neutralization. After immunization, a specific cellular response was observed 23 days after priming. Overall, the LNP formulation demonstrated better immunogenicity after administration of LNP RBD-hFc mRNA.

Testing-on-a-probe biosensors reveal association of early SARS-CoV-2 total antibodies and surrogate neutralizing antibodies with mortality in COVID-19 patients[2]

Yang et al. validate two novel biosensors for detecting early antibody response to SARS-CoV-2 infection and better predicting COVID-19 patient outcomes. Researchers developed two fast, automated, and highly sensitive biosensor assays for detecting SARS-CoV-2 antibodies in the first week after symptom onset. The first testing-on-a-probe (TOP) assay quantifies overall binding between the total SARS-CoV-2 antibodies (TAb) and the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, whereas the second detects the surrogate neutralizing antibodies (SNAb) that inhibit RBD attachment to angiotensin converting enzyme 2 (ACE2). The performance of TOP-TAb and TOP-SNAb was compared to the FDA-approved Roche Elecsys Anti-SARS-CoV-2 assay. In a 116 serum sample study, TOP-TAb was significantly more sensitive than the Roche assay, while TOP-SNAb was more sensitive than the Roche assay but the difference was not statistically significant. In another 120 patient study of day 0 serum samples, a higher percentage of patients that survived SARS-CoV-2 tested positive for TAb (63.6%) and SNAb (61.2%) than patients that died (34.4% for TAb and 24.1% for SNAb).

* Please note all studies published in medRxiv and bioRxiv are preprints and have not yet undergone a rigorous peer review process.

Broad and potent activity against SARS-like viruses by an engineered human monoclonal antibody[3]

Rappazzo et al. engineered a human monoclonal antibody against SARS-like sarbecoviruses to improve neutralization potency against SARS-CoV-2 and other SARS-like viruses which could become epidemic. Antibodies from the memory B cells of a 2003 SARS survivor were isolated, and directed evolution was utilized to obtain affinity-matured antibodies which had improved neutralization ability against SARS-CoV-2 S. The ADG-2 antibody was identified as a lead therapeutic candidate due to its potent neutralization activity of clade 1 sarbecoviruses, which included viruses with the potential for direct transmission to humans. Measurement of ADG-2's apparent binding affinity to 17 sarbecovirus receptor binding domains (RBD) showed that ADG-2 had high affinity to every clade 1 sarbecovirus RBD which had detectable hACE2 binding. Tests against naturally circulating SARS-CoV-2 variants with single amino acid substitutions in the RBD revealed that ADG-2 bound all 36 variants at 50% or more of WT SARS-CoV-2. Using an *in vivo* mouse model of SARS and COVID-19, prophylactic treatment with ADG-2 prior to challenge resulted in minimal weight loss, no change in Penh (measure of airway resistance), no signs of gross pathology, and prevention of viral replication. By these same variables, therapeutic use of ADG-2 after viral challenge was not as effective as prophylactic administration, but still more effective than the control.

CLINICAL PRESENTATION AND MANAGEMENT

Assessment of Maternal and Neonatal Cord Blood SARS-CoV-2 Antibodies and Placental Transfer Ratios[4]

Flannery et al. studied the placental transfer of SARS-CoV-2 IgG and IgM antibodies from mother to neonate during pregnancy. From April 9 to August 8, 2020, sera and cord blood samples were examined for 1,471 mother-newborn dyads after delivery in Pennsylvania Hospital in Philadelphia. Results showed that 83 (6%, 95% CI: 5%-7%) mothers were seropositive for IgG and/or IgM, 44 of whom tested positive by PCR for SARS-CoV-2 at some point during pregnancy, with a majority being asymptomatic. Of the seropositive women, 72 infants were seropositive, but only for IgG with no IgM detectable. IgM concentration was not significantly different in mothers with seropositive versus seronegative infants, and no seropositive infants were born to seronegative mothers. There was a positive correlation between IgG concentrations in maternal sera and cord blood, and a positive correlation between the transfer ratio for antibodies and increased time between positivity for SARS-CoV-2 and delivery. Transfer ratios were no different for positive women with symptoms versus no symptoms. It is concluded that the transmission of SARS-CoV-2 from mother to neonate during pregnancy is rare. Although transmission can occur after birth from mother or family members, there is potential for maternal antibodies against SARS-CoV-2 to provide protection to the neonate. These results can significantly inform vaccination timelines for pregnant women.

MENTAL HEALTH

Loneliness, worries, anxiety, and precautionary behaviours in response to the COVID-19 pandemic: A longitudinal analysis of 200,000 Western and Northern Europeans[5]

Varga et al. analysed survey data from Denmark, France, the Netherlands, and the UK to determine what effect lockdown interventions in each country had on the mental health of their respective citizens. The authors were particularly interested in loneliness, as that is well-documented as a common risk factor for depression and anxiety. They found that though people were worried in general about the pandemic, government announcements and interventions did not increase this worry. Across all countries, the level of anxiety was highest during March, when lockdown measures were initially implemented, but gradually decreased over time. A majority of participants reported being worried about someone they care about becoming sick. Young people (<30 years old), people who have been previously diagnosed with a mental illness, people diagnosed with a chronic illness, and women had higher levels of reported loneliness. By recognizing these more susceptible groups, the authors hope that in future pandemics or public health crises, the government can pay more attention to these groups and provide more focused interventions to help curb loneliness.

Association of Psychiatric Disorders With Mortality Among Patients With COVID-19[6]

In a retrospective cohort study, Nemani et al assessed the association between diagnosis of schizophrenia spectrum disorders, mood disorders, and anxiety disorders with mortality among patients who were positive for COVID-19 in a large medical system in New York. Of 7,348 laboratory-confirmed COVID-19 patients, 1% of patients had a history of schizophrenia spectrum illness, 7.7% of patients had a history of a mood disorder, and 4.9% had a history of an anxiety disorder. The authors found that premorbid diagnosis with a schizophrenia spectrum disorder was associated with increased risk of mortality (aOR: 2.67). Mood disorders and anxiety disorders were not associated with mortality after adjustment for demographic and medical risk factors.

NON-CLINICAL TRENDS

Managing Multimorbidity (Multiple Chronic Diseases) Amid COVID-19 Pandemic: A Community Based Study From Odisha, India[7]

Researchers studied the effect of an 8-week COVID-19 lockdown in Khurda district of Odisha, India on management of multimorbidity. Using a cross sectional design and statistical analysis, researchers interviewed 600 people (300 urban, 300 rural). The mean age of participants was 55 and average duration of chronic diseases was 9 years. Data showed that hypertension was the most common disease (44%), followed by diabetes (36%, more prevalent in urban areas), musculoskeletal morbidities (15%, more prevalent in rural areas) and acid peptic diseases (9%, more prevalent in rural). Overall, around 40% of participants had multimorbidity (122 urban, 115 rural). During the lockdown, changes in routine-checkups were most altered for those with multimorbidity, with statistically significant differences seen in changes in daily routine, worse physical activity, worse continuation of treatment, and dietary changes more prevalent for urban versus rural dwellers. Additionally, those with multimorbidity faced more challenges in managing diseases, with most pressing issues of physician consultation and diagnostic investigations. Factors that influenced this included transportation, financial, and mobility

issues, and fear of getting COVID-19 during the lockdown. Additionally, females and younger individuals were more likely to face challenges than males. Finally, physical and mental health were worse for those with multimorbidity. These results show that efforts should be taken during the COVID-19 pandemic to mitigate the worse effects of multimorbidity, with telemedicine, self-care, and patient education.

Association of intensive care unit patient load and demand with mortality rates in US Department of Veterans Affairs hospitals during the COVID-19 pandemic[8]

The authors studied mortality and ICU patient load data of 88 VA hospitals, with 8516 total COVID-19 patients, from March to August 2020. The average age of the COVID-19 patients was about 68 years old, and 94% were men. Mortality of COVID-19 patients in the ICU ranged from the lowest in July 2020 with 12.5% of patients dying to the highest in April 2020 with 25% of patients dying. Below 75% ICU capacity, there was no significant difference in mortality. At 75-100% capacity, mortality was almost double (HR= 1.94) compared to a demand of <25%. These findings reinforce the need to decrease the patient load and demand in the ICU in order to decrease mortality among COVID-19 patients who are treated in the ICU.

PHARMACEUTICAL INTERVENTIONS

Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine[9]

This study was a multicenter, placebo controlled, phase 1-2a trial to evaluate the safety, reactogenicity, and immunogenicity of the candidate vaccine Ad26.COV2.S; healthy adults in two age cohorts were randomly assigned to receive the vaccine at a low dose, high dose, or placebo in a single-dose or two-dose regimen. This interim analysis found that the Ad26.COV2.S vaccine had an acceptable safety profile, an acceptable reactogenicity profile, and was immunogenic after a single low dose or a single high dose. The most frequent adverse events were fatigue, headache, myalgia, and injection-site pain; additionally, fever was the most frequent systemic adverse event. These interim results support the continued development of this vaccine candidate.

Single Dose Administration, And The Influence Of The Timing Of The Booster Dose On Immunogenicity and Efficacy Of ChAdOx1 nCoV-19 (AZD1222) Vaccine[10]

The University of Oxford's ChAdOx1 nCoV-19 vaccine is a monovalent chimpanzee adenovirus vector. After initial attempts of single dose administration in 17,177 participants, the researchers determined that two doses would more effectively develop protective antibodies. Because some participants decided not to get the second dose, the researchers were able to compare the effect of one versus two doses, as well as how the timing of the second vaccine impacted vaccine efficacy (VE). The single dose showed a 76% protection against symptomatic COVID-19 within the first 90 days, but only showed 16% protection against asymptomatic infection. Within the first cohort that received the second dose (LD/SD), VE was 80.7% 14 days after the second dose. This is higher compared to the group that received the standard dosing (SD/SD), for which VE was 63.1% after 14 days. Among SD/SD, VE jumped from 54.9% to 82.4% when the second dose was given 6-8 and 12 weeks after the first dose, respectively. Participants who received the vaccine more than 12 weeks apart also showed double the antibody titres compared to those who received the vaccine after 6 weeks. Considering current and future vaccine shortages, the authors suggest that countries using the Oxford vaccine may benefit from adopting the 12-week

vaccination program to help reach herd immunity and increase vaccine efficacy and antibody titres.

Demographic Characteristics of Persons Vaccinated During the First Month of the COVID-19 Vaccination Program — United States, December 14, 2020–January 14, 2021[11]

Painter et al. reported on the demographic characteristics of individuals vaccinated from December 2020 to January 2021 after the U.S. COVID-19 vaccination program in December 2020 authorized both Moderna and Pfizer-BioNTech vaccines as an urgent intervention to control COVID-19. Due to limited supply, health care personnel and long-term care facilities' (LTCF) residents and staff were prioritized for the vaccination launch. Approximately 12,928,749 individuals across 64 jurisdictions and five federal entities in the United States were vaccinated in one month. This group was 63% women, 55% aged ≥50 years, and 39.6% racial and ethnic minorities (52% did not provide race/ethnicity data). Although the authors note limitations regarding generalizability, these results suggest the need for public health officials to make efforts to ensure equitable and efficient vaccine distribution to communities disproportionately affected by the virus, such as non-Hispanic Black (Black), non-Hispanic American Indian/Alaska Native (AI/AN), and Hispanic persons.

The safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia[12]

This study explored the preliminary efficacy results from a phase 3 trial of the heterologous recombinant adenovirus (rAd)-based vaccine, also known as Gam-COVID-Vac (Sputnik V). This COVID-19 vaccine is typically stored at -18°C but is able to be stored between 2°C to 8°C. The trial was randomised, double-blinded, and placebo-controlled, and participants were at least 18 years old, with 87 years as the oldest reported age. From September 7 to November 24 2020, 19,866 individuals received two doses of either the vaccine or the placebo, which were given 21 days apart. The findings demonstrated 91.6% efficacy, and immunogenicity analysis confirmed that the Sputnik V vaccine successfully created an antibody response. Common side effects of the vaccine included flu-like symptoms, headache, fatigue, and inflammation at the site of injection. There were a total of 7966 adverse events, and 94% of these were considered mild. No serious adverse events or deaths were associated with the vaccine. Overall, this trial demonstrates promising results for Sputnik V, and it is now being tested as a single-dose vaccine trial.

SAMPLING EFFORTS

Standardization of ELISA protocols for serosurveys of the SARS-CoV-2 pandemic using clinical and at-home blood sampling[13]

NIH Researchers outline the development of an ELISA-based serology assay protocol that measures antibodies against coronavirus proteins to better predict the prevalence and understand the spread of COVID-19. The protocol standardizes thresholds of IgG, IgM, and IgA antibodies in multiple sample types with high specificity and sensitivity. The researchers used purified antigens to compare to currently available antigens to

determine which combination is the most sensitive to SARS-CoV-2. Through careful statistical evaluations, the researchers determined that using a combination of the McLellan/VRC spike construct and the Ragon RBD in the assay gave the most sensitive results. While there is a manual protocol, the researchers also developed a semi-automated protocol that increases the speed of processing and standardization to maintain consistency and increase throughput. Both methods resulted in a 100% sensitivity and specificity at three standard deviations above negative control values. This protocol utilizes common reagents and instruments such that this protocol can be easily adapted to other labs. However, validation steps must be done to account for variances in equipment.

SCREENING AND TESTING

Evaluation of the practicability of a finger-stick whole-blood SARS-Cov-2 self-test adapted for the general population[14]

A recent study demonstrated the high sensitivity and specificity of AAZ COVID-PRESTO, a Point of Care (POC) COVID-19 diagnostic test. Prazuck et al. thus aimed to evaluate users' ability to obtain and interpret test results from the COVID-PRESTO and to understand its efficacy outside a laboratory setting. Non-medically trained participants (n=143) were recruited from four sites in Central France between March and April 2020. Participants viewed instructional media on using the self-test, administered the test and filled out satisfaction questionnaires. Participants were also asked to interpret standardized test results. The written and video instructions were found to be comprehensible by 88.5% and 90.7% of the participants, respectively. Nearly all participants (98.6%), were able to obtain a valid test result, and 94.3% of participants were satisfied with the COVID-PRESTO POC test, rating it as "good," "very good", or "excellent." Out of the 288 tests read by participants in their assessment, the success rate was 99.3% (only two were interpreted incorrectly). Age and education were not found to significantly impact the level of instruction comprehension or test usability. Authors conclude that COVID-PRESTO demonstrates potential as a POC test for the wider public.

TRANSMISSION PATTERNS

First report on prevalence of SARS-CoV-2 infection among health-care workers in Nicaragua[15]

Huete- Pérez et al. aimed to estimate the prevalence of SARS-CoV-2 among healthcare workers in Nicaragua in light of government restrictions on testing and supplies. Participants included physicians, nurses and medical assistants from public and private hospitals. Saliva specimens were self-collected and sampled using a loop-mediated isothermal amplification assay (LAMP). Findings demonstrated that 30.35% of those tested were infected with SARS-CoV-2 between June 22 - July 22, 2020. Over half (54.92%) of cases were asymptomatic and continued to treat patients. A third (30.33%) of cases reported at least one comorbidity. Male sex and being between the ages of 30-40 served as risk factors for testing positive for SARS-CoV-2. While 94.97% of participants at private hospitals reported PPE use, 81.82% of participants at public hospitals used PPE. Authors suggest that LAMP assays may be a suitable testing approach for case detection in Nicaraguan and other Latin American settings. These findings demonstrate the rapid spread of COVID-19 in the absence of effective pandemic control policies.

SARS-CoV-2 antibody seroprevalence in India, August-September, 2020: findings from the second nationwide household serosurvey[16]

Murhekar et al. conducted a nationwide household serosurvey consisting of 29,082 individuals from August to September 2020 to assess the seroprevalence of SARS-CoV-2 across India. Survey participants included individuals above the age of 10 years throughout 700 cluster regions, both rural and urban, within 70 districts across 21 states in India. Data was collected regarding participant sociodemographic, symptoms related to COVID-19 (eg. fever, cough, new loss of taste or smell, etc.), and history of COVID-19 exposure and illness by testing blood serum samples for SARS-CoV-2 IgG antibodies. 48.8% of participants were female, 74% lived in rural areas, 22.8% were aged 45-60 years, and 14.7% had occupations with high risk of COVID-19. 25,947 out of the 29,092 participants tested negative for the presence of IgG antibodies against SARS-CoV-2. Seroprevalence was found to be higher in urban areas than rural with no difference across occupations, age, or sex; and 3.2% of seropositive individuals reported having a history of symptoms related to COVID-19. Additionally, the results suggest that 7% of the population in India above the age of 10 years had been exposed to SARS-CoV-2 since the start of the study. When comparing results to the prior national survey, the results suggest particularly high-levels of transmission within rural areas. The authors' future recommendations for better containing COVID-19 in India involve continued intervention to control transmission in rural areas, expansion of testing, and continued national serosurveys to enhance understanding of at-risk populations in India.

ADDITIONAL RESOURCES
UCSF Library COVID-19 Research and Information Resources
UCSF Institute for Global Health Sciences COVID-19 Resources
UC Davis One Health Institute COVID-19 FAQs
Harvard Viswanath Lab Myths vs Facts
Accesocovid.com

Note on this Document: This document was assembled by undergraduate and doctoral students attending the University of California, Los Angeles and the University of California, San Francisco with the intent of facilitating the rapid dissemination of information to the global community. Anya Bekhtel, Alyssa Bercasio, Alicya Burt, Amanda Chan, Diana Etwaru, Sarah Gallalee, Shivali Joshi, Anika Kalra, Emily Ng, Brooke Jackson, and Lina Salam contributed to these summaries. This work is volunteer based.

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