The SARS-CoV-2 Spike Protein and Neutralizing Antibody: Role of the Spike Protein Receptor-Binding Domain (S1-RBD)

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Advancements in this fast-moving field may appear after printing of this document. Also, it should be noted that medRxiv articles are not yet peer reviewed.
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Glossary of Terms and Background

Immunity: If a person is immune to a pathogen (such as potentially the severe acute respiratory syndrome-coronavirus-2 [SARS-CoV-2]), they can be exposed to it without becoming infected (or may experience more mild disease/faster resolution). Both innate and adaptive mechanisms can contribute to immunity.1,2 Adaptive immunity is specific for a pathogen and can involve both humoral (antibody [Ab]) and cellular components (e.g., T-cells). Protection may be mediated largely by Ab in some infections, while others require elements of cellular immunity such as helper and killer T-cells and still others failing to induce immunity to reinfection (example syphilis or HCV).

While many Abs result from infection, only a small subset (if any) are typically neutralizing. Neutralizing Abs to the spike protein receptor-binding domain (S1-RBD) (see “Structural Proteins” section below) may account for up to 90% of the neutralizing Ab in SARS-CoV-2.3 Quantitative Ab tests for neutralizing Ab offer significant clinical utility, especially if a defined immunity threshold is identified.

Quantitative antibody test: Defines the level (amount) of Ab present. If an immunity threshold is determined, use of a quantitative test (example anti-HBsAg at 10 mIU/ml) supports rapid assessment for protection/vulnerability. As Ab levels can wane over time (some very rapidly and others very slowly), quantitative assessment can be very useful. True quantitation requires an accepted international standard utilized by all manufacturers for a shared (common) threshold value. In the absence of such a standard, tests are technically semi-quantitative, meaning the value is only relevant to that assay. However, “quantitative” is often applied to both quantitative and semi-quantitative tests.

Qualitative antibody test: A “yes” or “no” answer whether Ab is present independent of how much by identifying a value to define a “positive” from a “negative” population. Some qualitative tests can be semi-quantitative if linearity in the reporting range is established relative to the internal standard used.

SARS-CoV-2: Antibody to structural proteins: SARS-CoV-2 has 4 major structural proteins (Fig. 1). Infection usually (but not always) results in the production of Abs to Nucleocapsid Protein (N-protein) and the transmembrane Spike glycoprotein (S-glycoprotein or S-protein). S-protein comprises 2 regions: S1 and S2 (Fig. 2). S1 mediates binding to the host cell expressing the ACE-2 receptor using the S1-RBD. S2 then mediates fusion and entry for viral reproduction. Antibody produced to these differing targets can vary between patients.5 Severe illness is often associated with higher levels of Ab vs. mild or asymptomatic disease.3,6,7
**Nucleocapsid protein (N-protein):** The structural protein associated with the viral RNA inside of the cell. N-protein is the most abundant viral protein and is highly immunogenic. Antibodies to N-protein result from infection in almost all patients.

**Spike protein receptor-binding domain (S1-RBD):**
S-protein is highly immunogenic and Abs to RBD and other Spike epitopes result from infection in almost all patients.

**Binding vs. neutralizing antibodies:** All Abs formed to parts (epitopes or antigens) of SARS-CoV-2 are binding, but only a subset also exhibit neutralizing activity.

**Neutralizing antibody:** The ability of an Ab to inhibit/prohibit infection, often by interfering with binding to the host cell. In viral infections, this is typically assessed in-vitro using techniques such as plaque reduction neutralization tests (PRNT) or alternate approaches such as pseudoviral constructs that incorporate key viral components vs. live virus to assess for inhibition of binding. These methods support evaluation of the ability of specific Abs to interfere with viral attachment or infection, and frequently (but not always) are a surrogate for protective immunity. Multiple studies indicate a primary role for neutralizing Ab targeted to epitopes in the S-protein of SARS-CoV-2, with Abs to S1-RBD epitopes estimated to comprise ~90% of neutralizing activity. Neutralization techniques characteristically assess for percent inhibition (e.g., 50% or 90%) associated with specific Ab titers or values. Antibodies from serum or plasma as well as purified Abs (including monoclonal) can be evaluated for neutralization.

**Two common types of neutralization tests are conducted in SARS-CoV-2:**
1. Virus neutralization tests (VNT), such as the plaque-reduction neutralization test (PRNT) and microneutralization, using live SARS-CoV-2 virus. This testing usually requires a biosafety level-3 (BSL-3) laboratory and may take several days to complete.
2. Pseudovirus neutralization tests use recombinant pseudoviruses (like vesicular stomatitis virus, VSV) that incorporate the S-protein of SARS-CoV-2 and assesses for inhibition of binding the viral receptor. These approaches are often more rapid, and many can be conducted in a less stringent BSL-2 setting.
3. Other techniques for assessing neutralization with SARS-CoV-2 antibodies have also been described, including a high throughput format.

**Vaccines and neutralizing antibody:** Multiple vaccines employing a wide range of technologies are currently in development, with some advancing to phase 3 or even under limited deployment. Most if not all include assessment for neutralizing Ab, and many also assess for evidence of cellular immunity. While abundant evidence of neutralization now exists for Ab to the S1-RBD, phase 3 vaccine trials are expected to identify if these Abs confer immunity/resistance. If so, quantitative assessment may prove salient to immunity resulting from natural infection or vaccination as well as the need to boost if declining immunity with decreases in neutralizing Ab are confirmed.
SARS-CoV-2 and Neutralizing Antibodies

Mapping neutralizing and immunodominant sites on the SARS-CoV-2 spike 2 receptor-binding domain by structure-guided high-resolution serology.


- Spike (S)-glycoprotein is the main target of neutralizing Abs and the basis for vaccine design.
- Six hundred and forty-seven SARS-CoV-2 subjects (hospitalized, symptomatic, asymptomatic): Higher S and N IgG and IgA titers were found in hospitalized vs. non-hospitalized/asymptomatics. A strong Ab response against N-protein was demonstrated but anti-N Abs are not neutralizing.
- RBD was found to be the main target of neutralizing Abs in plasma of convalescent patients by depleting plasma of Abs to RBD and obtaining neutralization titers before and after Ab depletion.
- “We found that an almost complete depletion of RBD-specific Abs from 21 plasma samples reduced SARS-CoV-2 neutralizing titers by ~90% on average.”
- RBD-specific Abs in patient serum or plasma inhibited binding of SARS-CoV-2 RBD to ACE2 in the majority of hospitalized patients; RBD Abs from hospitalized inhibited binding more than those from non-hospitalized/asymptomatics.
- SARS-CoV-2 anti-RBD Abs accounted for the majority of IgG responses with much lower titers found to S2 or S1 domain A.
- Found a progressive decay in Ab titers that did not mirror the increase in Ab titers blocking binding to ACE2.

The receptor binding domain of the viral spike protein is an immunodominant and highly specific target of antibodies in SARS-CoV-2 patients.


- Study using a large panel of human sera (63 SARS-CoV-2 patients and 71 control individuals) and hyperimmune sera from animals exposed to zoonotic CoVs to evaluate RBD’s performance as an antigen for reliable detection of SARS-CoV-2–specific Abs.
- By day 9 after the onset of symptoms, the recombinant SARS-CoV-2 RBD antigen was highly sensitive (98%) and specific (100%) for Abs induced by SARS-CoVs.
- Observed a strong correlation between levels of RBD-binding Abs and SARS-CoV-2 neutralizing Abs in patients.
- Results establish that most individuals, including people who have been recently exposed to acute common HCoV infections, do not have detectable levels of cross-reactive Abs to the recombinant RBD of SARS-CoVs.

Key takeaway
Depleting plasma of RBD Abs led to ~90% decrease in neutralizing titer, indicating that the RBD elicits most neutralizing Abs.

Key takeaway
The early kinetics of SARS-CoV-2 Ab responses support using the RBD antigen in serological diagnostic assays and RBD-specific Ab levels as a correlate of SARS-CoV-2 neutralizing Abs in people.
Detection of SARS-CoV-2-Specific Humoral and Cellular Immunity in COVID-19 Convalescent Individuals.

- Most convalescent COVID-19 patients (13 of 14 tested) displayed evidence of neutralizing Abs.
- Focused on seroconversion Ab to N-protein and S1-RBD and assessed neutralizing activity using a pseudo-virus particle-based neutralization assay.
- A significant correlation between neutralizing Ab titers and AUC of anti-S-RBD IgG, but not of anti-N-protein IgG was observed.

Key takeaway
Antibody to S1-RBD but not Ab to N-protein is associated with neutralization ability.


- COVID-19 (1,850) patients were investigated for dynamic changes of the total Ab, Ab to S1-RBD, and Ab to N-protein during recovery.
- IgG production was delayed in those with severe disease compared to mild/moderate disease, but hospitalized patients had higher levels of Ab. Decreases in Ab levels in hospitalized patients were associated with poorer outcomes.
- Virus-free patients displayed 2-fold higher levels of RBD- and S-specific IgG while patients with low levels of these Abs were subject to reinfection. In particular, the anti-RBD IgG level was much higher in virus-free patients. The authors concluded these Abs play an important role in viral clearance/protection.
- Additional note: A Total test (IgM and IgG) was more sensitive than just IgM or IgG during the first week of symptomatic infection.

Key takeaways
- Testing for anti-S or anti-RBD IgG is suggested but no similar recommendation is made for anti-N-protein. Quotes include:
  - “Overall, our results suggested that these IgGs, especially S-specific or RBD-specific IgG played an important role in virus clearance and recovery of COVID-19 patients.”
  - “Thus, it is important to test the S-specific or RBD-specific IgG level before discharging patients and keep close monitoring of the patients with a low level of protective antibody.”
Testing for responses to the wrong SARS-CoV-2 antigen?

- Five hundred and eleven patients and hospital staff with binding ratios between 0.25 and 1.4 (undetectable levels) tested with the Abbott SARS-CoV-2 IgG assay were tested with anti-RBD ELISA that detects total Abs; 294 of these 511 patients (58%) had detectable anti-RBD Abs

Key takeaways
Clinicians should be aware of the design of SARS-CoV-2 assays. Not all assays detect the same antigen-generated Abs in the patient. The author concludes that the
- “anti-nucleocapsid protein assay is insensitive in the field”, and
- “does not indicate accurately the presence of neutralizing and potentially protective antibodies in the convalescent individual.”

Other Publications

Rapid generation of neutralizing antibody responses in COVID-19 patients.

Kinetics and isotype assessment of antibodies targeting the spike protein receptor binding domain of SARS-CoV-2 in COVID-19 patients as a function of age and biological sex.

Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike.

Perspectives on therapeutic neutralizing antibodies against the Novel Coronavirus SARS-CoV-2. (Review Article)

Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications.

Broad neutralization of SARS-related viruses by human monoclonal antibodies.
SARS-CoV-2 and Serosurveillance/Seroprevalence

Humoral response dynamics following infection with SARS-CoV-2.

- The mean estimated half-life of the Ab to N-protein was 52 days. The S-protein and RBD Ab had significantly longer mean half-lives of 81 days and 83 days, respectively.
- The slower decay of the SARS-CoV-2 S-protein Ab identified in this study makes assays to the S-protein a more reliable target for serological assays in the longer term.
- An ACE-2-receptor competition assay demonstrated significant correlation between the S and RBD-Ab titers and ACE2-receptor blocking in-vitro.

Detection, prevalence, and duration of humoral responses to SARS-CoV-2 under conditions of limited population exposure.

- Inclusion of multiple independent assays markedly improved the accuracy of Ab tests in low seroprevalence communities and revealed differences in Ab kinetics depending on the viral antigen.
- The correlation was strong between RBD-reactive IgG and plaque reduction neutralization test titers, which were quantified as the final dilution at which 90% viral neutralization occurred.
- RBD- and S2-specific and neutralizing Ab titers remained elevated and stable for at least two to three months post-onset, whereas those against N-protein were more variable with rapid declines in many samples.

Longitudinal analysis of clinical serology assay performance and neutralising antibody levels in COVID19 convalescents.

- The sensitivity of the Abbott ARCHITECT SARS-CoV-2 IgG assay declined to 85% in between 61–80 days, and 71% at >81 days post diagnosis. Conversely, the sensitivity of the Siemens Healthineers Atellica IM SARS-CoV-2 Total assay increased over time. Therefore, the Abbott assay is not appropriate for seroprevalence studies, for identification of SARS-CoV-2 naive vaccine trial participants, or for investigation of individuals presenting with long term chronic symptoms.
- 14/91 participants that were positive on the Abbott assay at visit 1 were negative by visit 3 or 4, whereas none of the participants with a positive result at visit 1 on the other assays including Siemens Healthineers became negative at visit 3 or 4.
- The use of serological assays that use S-based antigens and correlate best with neutralization (NT50) measurements, such as the Siemens Healthineers assay, would appear most appropriate for prognostication of immunity.

Key takeaway
- Widely used serological tests that depend on Ab to N-protein may therefore significantly underestimate the prevalence of infection following the majority of infections.
- Virus neutralization is durable for at least several months after SARS-CoV-2 infection based on the elevation and stability of RBD and S2-specific and neutralizing Ab titers.
- Overall, given their superior sensitivity at each of the time points investigated thus far, the Siemens Healthineers Atellica SARS-CoV-2 Total assay and Roche ELECSYS Anti-SARS-CoV total antibody assay appear most appropriate for diagnosis of prior SARS-CoV-2 infection, at least within 4 months of SARS-CoV-2 infection, and would report a higher population prevalence than Abbott SARS-CoV-2 IgG assay or DiaSorin LIASON SARS-CoV-2 IgG assay in the 1 to 4 month post-infection period.
Changes in SARS-CoV-2 antibody responses impact the estimates of infections in population-based 2 seroprevalence studies.


- As compared to anti-S-protein Ab responses, those against the N-protein appear to wane in the post-infection and substantially underestimated the proportion of SARS-CoV-2 infections in the groups of patient positive contacts.
- A good correlation in the proportion of seropositive individuals was observed between tests detecting Ab responses against the trimeric and/or monomeric S-proteins while a poorer correlation was observed with those detecting anti-N-protein Ab responses.
- 40% of asymptomatic individuals became seronegative over time likely due to waning of the anti-N-protein Ab responses rather than to a global reduction of the SARS-CoV-2 Ab response.

Key takeaway

These results provide new insights in the evolution of the SARS-CoV-2 Ab response from the acute to the post-infection phase and indicate that the detection of Ab responses against the native trimeric S-protein should be implemented to avoid large underestimation of SARS-CoV-2 infections in population-based seroprevalence studies.

Other Publications

(Some of these articles have findings that also apply to the section above.)

Prevalence of SARS-CoV-2 antibodies in a large nationwide sample of patients on dialysis in the USA: a cross-sectional study.

A serological assay to detect SARS-CoV-2 seroconversion in humans.

Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study.

Heterogeneous antibodies against SARS-CoV-2 spike receptor binding domain and nucleocapsid with implications on COVID-19 immunity

The RBD of the spike protein of SARS-group coronaviruses is a highly specific target of SARS-CoV-2 antibodies but not other pathogenic human and animal coronavirus antibodies.

Long period dynamics of viral load and antibodies for SARS-CoV-2 infection: an observational cohort study.
SARS-CoV-2 and Vaccines

SARS-CoV-2 vaccines currently in phase 3 trial in the U.S. induce neutralizing Abs (Note, the following describe studies for the 4 current vaccines in phase 3 trials in the U.S.: Moderna; Pfizer/BioNtech; Johnson & Johnson; and Astra Zeneca/Oxford which is currently on pause in the U.S.)

Modalities:
• Moderna and Pfizer/BioNtech: mRNA
• Astra Zeneca and Johnson & Johnson: Adenovirus vector

Moderna vaccine candidate mRNA encoding the S-protein (Phase 1).
An mRNA Vaccine against SARS-CoV-2 — Preliminary Report.

• Forty-five healthy adults (ages 18-55 years).
• mRNA-1273 encodes stabilized prefusion SARS-CoV-2 S-protein.
• No adverse events were trial-limiting—occurring in over half of subjects as fatigue, chills, headache, myalgia, and pain at the injection site, and were more common after the second vaccination, especially for highest dose.
• At day 43, neutralizing activity was detected in all subjects.
• Good correlation between binding assays for spike trimer (S-2P) and RBD and neutralizing activity by pseudovirus neutralization assay (PsVNA) and PRNT.

Key takeaway
Phase 1 clinical trial S-protein and RBD binding results and results of neutralization tests support the continuation of this vaccine development (now in phase 3 clinical trials).

Moderna vaccine (mRNA encoding the S-protein) (Preclinical mouse study).
SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness.

• Vaccine (mRNA 1273) induced both potent neutralizing Ab responses and CD8 T cell responses. Vaccine protected against SARS-CoV-2 infection in the lungs and noses of mice.
• Vaccine elicited dose-dependent S-specific binding Abs in all mouse strains. Potent pseudovirus neutralizing activity was demonstrated.
• Two 1 µg doses protected mice from viral replication in lungs.
• The level of neutralizing activity induced by vaccine (1 µg) in mice was similar to that induced in humans by vaccine (100 µg)—the dose chosen for mRNA-1273 to advance into phase 3 clinical trials.

Key takeaway
This preclinical study supports advancement of this vaccine (100 ug dose) to phase 3 clinical trials.

Pfizer and BioNtech vaccine (mRNA encoding the S receptor-binding domain) (Phase 1/2).
Phase 1/2 study to describe the safety and immunogenicity of a COVID-19 RNA vaccine candidate (BNT162b1) in adults 18 to 55 years of age: Interim report.

• Forty-five adults (18-55 years of age).
• mRNA encoding the RBD in a lipid nanoparticle.
• Three dose groups: 10, 30, 100 µg.
• Two doses 31 days apart.
• Measure of response: Anti-RBD and ability to neutralize.
• “RBD-binding IgG concentrations were detected at 21 days after the first dose and substantially increased 7 days after the second dose given at day 21.”

Key takeaway
These phase 1/2 study results support continuation of this vaccine development (now in phase 3 clinical trials).
**Pfizer and BioNTech vaccine (mRNA encoding full-length S-protein) (Full Phase 1).**

RNA-based COVID-19 vaccine BNT162b2 selected for a pivotal efficacy study.


- Healthy adults (18-55 or 65-85 years of age).
- mRNA encoding RBD, and mRNA encoding full-length S-protein.
- Two injections, 21 days apart: RBD, or S-protein, or placebo.
- Full-length S-protein was chosen "The primary consideration...was the milder systemic reactogenicity profile of BNT162b2 (full-length S-protein) particularly in older adults, in the context of comparable antibody elicited by both candidate vaccines."

**Key takeaway**

BNT162b2 (RNA vaccine encoding prefusion stabilized membrane-anchored SARS-CoV-2 full-length S-protein) at the 30-μg dose level was chosen to progress into the Phase 2/3, global safety and efficacy clinical trial.

**Astra Zeneca/Oxford (Chimp adenovirus vector full-length S-protein) (Phase 1/2).**

Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial.


- Subjects (1077, ages 18-55 years).
- Adenovirus-based vaccine expressing full-length S-protein (ChAdOx1 nCoV-19.)
- 2 doses 28 days apart.
- Anti-S IgG tested for response and neutralization assessed.
- 32/35 (91% had neutralizing Abs after one dose and 100% after the second dose).
- "Neutralizing Ab responses correlated strongly with Ab levels measured by ELISA."
- Note: Two participants with severe neurologic manifestations have been identified as of Sept. 18, 2020. Reports indicate one may be a case of undiagnosed multiple sclerosis unrelated to the vaccine and the other may be a case of transverse myelitis. The trial is currently on hold in the U.S. (as of Sept.25, 2020) but has resumed outside the U.S. The construct utilizes a chimp adenoviral vector that is novel for use in a human vaccine.

**Key takeaway**

The vaccine candidate chimpanzee adenovirus-vectorized vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 S-protein elicited neutralizing Ab responses that correlated strongly with Ab levels. The trial is currently on hold in the U.S. (as of Sept. 25, 2020) but has resumed outside the U.S.

**Johnson and Johnson (adenoviral vector full-length S-protein). (Preclinical nonhuman primates).**

Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques.


- Adenovirus-vector based vaccine (AD26) expressing full-length S-protein.
- Fifty-two rhesus macaques were immunized with vaccine or control and followed by SARS-CoV-2 challenge.
- Vaccine-induced neutralizing Abs that correlated with protection. Serum Ab titers are potential correlates of protection for this virus.
- "We observed RBD-specific binding antibodies by ELISA in 31 of 32 vaccinated animals by week 2 and in all vaccinated animals by week 4."

**Key takeaway**

This adenovirus serotype 26 (Ad26) vector-based vaccines expressing the SARS-CoV-2 S-protein shows protection in nonhuman primates after a single-shot.
**Novavax vaccine (Adenovirus vector full-length S-protein) (Phase 1/2).**

**Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine.**


- "NVX-CoV2373 is a recombinant rSARS-CoV-2 nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 S-glycoproteins and Matrix-M1 adjuvant.
- Examined efficacy of 5-μg and 25-μg doses, with or without Matrix-M1 adjuvant, in 131 healthy adults (83 vaccine with adjuvant; 25 no adjuvant); 23 placebo.
- Phase 1: two intramuscular injections, 21 days apart. Primary analysis was performed at day 35.
- Adverse events were mild in most subjects; no severe adverse events.
- “…vaccine induced high immune responses, with levels of neutralizing antibodies that closely correlated with anti-spike IgG.” Adjuvant enhanced immune responses; induced T-helper 1 (Th1) response.
- Two doses of 5 ug with adjuvant induced neutralization responses that were higher than those in convalescent serum from most symptomatic patients.

**Russia National Research Center vaccine (adenovirus carrying full-length S-protein) (Phase 1/2).**

**Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia.**


- Vaccine is a recombinant adenovirus type 26 (rAd26) vector and a recombinant adenovirus type 5 (rAd5) vector, both carrying the gene for SARS-CoV-2 S-glycoprotein (rAd26-S and rAd5-S). Safety and immunogenicity of two formulations (frozen and lyophilized) of this vaccine were assessed.
- Seventy-six volunteers enrolled (38 for lyophilized and 38 for frozen vaccine). Vaccine was administered intramuscularly on day 0; either one dose of rAd26-S (9 volunteers) or one dose of rAd5-S (another 9 volunteers). Safety was assessed for 28 days.
- Five days later two-step vaccine was administered intramuscularly (rAd26-S given on day 0 and rAd5-S on day 21) (20 volunteers). “use of a heterologous prime-boost immunization, when rAd26-S is used for priming and rAd5-S is used for boosting, is an effective approach to elicit a robust immune response and to overcome the immune response that is formed to the components of a viral vector.”
- Vaccines were well tolerated. Most adverse events were mild. No serious adverse events.
- All volunteers made Abs to SARS-CoV-2 and induced strong RBD-specific IgG titers, and neutralizing Ab response comparable to that of convalescent plasma.

**Key takeaway**

The results of this phase 1 study support continuation of this vaccine development (now in phase 2 and in preparation for 3 clinical trials).
China vaccine (adenovirus type-5 [Ad5] vectored expressing full-length S-protein) (Phase 1).

**Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomized, first-in-human trial.**


- First report (108 patients) on immunogenicity for a recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine expressing the full-length S-glycoprotein of SARS-CoV-2. Safety, tolerability, and the ability to induce neutralizing Ab were assessed. Most adverse reactions were fever (50 [46%]), fatigue (47 [44%]), headache (42 [39%]), and muscle pain (18 [17%]). No serious adverse events were noted 28-days post injection.
- Neutralizing Abs increased significantly at day 14 and peaked 28 days post-vaccination.
- At least a four-fold increase of anti-RBD Abs was noted in 35 (97%) of 36 participants in the low-dose group, 34 (94%) of 36 in the middle-dose group, and 36 (100%) of 36 in the high-dose group.
- Neutralizing Abs against live SARS-CoV-2 were all negative at day 0, and increased by day 14, and peaked at 28 days post-vaccination. Concordance between anti-RBD and anti-S levels and neutralization activity was observed (a little higher for the anti-RBD).
- A single dose of Ad5 vaccine elicited a four-fold increase in binding Abs to RBD in 94–100% of participants.

**Approaches and challenges in SARS-CoV-2 vaccine development.**


- This review focuses on SARS-CoV-2 vaccine development with respect to antigen selection and engineering, preclinical challenge studies, and immune correlates of protection.
- Monoclonal Ab studies have demonstrated that SARS-CoV-2-infected humans develop potent neutralizing Ab responses against S and especially the RBD.
- On the other hand, vaccination with vaccines expressing N-protein did not result in protection against SARS-CoV challenge. (Note the authors were discussing animal models and SARS-CoV).
- In rabbits immunized with RBD, S1, S2, and modified variants, RBD elicited five times higher affinity Abs than other immunogens.
- Protection is often correlated with neutralizing Ab activity.
- Rats immunized with SARS-CoV-2 RBD developed a strong neutralizing Ab response.

**Other Publications**

**SARS-CoV-2 vaccines: Status report.**

**COVID-19 vaccine BNT162b1 elicits human antibody and T(H)1 T-cell responses.**

**Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses.**

**Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody.**

**Developing a low-cost and accessible COVID-19 vaccine for global health.**
References:
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