Viral Variants and Vaccines COVID-19

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Viral mutations may naturally occur anywhere in the SARS-CoV-2 genome. Unlike the human DNA genome, which is slow to mutate, RNA viruses are able to readily, and quickly, mutate. A mutation may alter the viral function (eg, enhance receptor binding), or may have no discernable function.
The CDC predicts the **B.1.1.7 variant** (first detected in the United Kingdom) will be the major circulating variant in the United States by March 2021. https://www.nytimes.com/2021/01/15/health/covid-cdc-variant.html

Enhanced genomic surveillance in some countries have detected other variants of concern (VOCs) including **B.1.351 (501Y.V2)** first detected in South Africa and the **B.1.1.28 (renamed P.1) (501Y.V3)** which was detected in 4 travelers from Brazil during routine screening at the Tokyo airport. https://www.reuters.com/article/us-health-coronavirus-japan-variant-idUSKBN29F08R
[20]
As of January 2021, researchers are studying how variants may or may not alter the extent of protection by available vaccines.
The immune response provoked by vaccines includes protection from the antigen by eliciting antibodies, T-cells, and interferons.
Variants that have emerged in the United Kingdom and South Africa in late 2020 have multiple mutations in their S glycoproteins (ie, the spike protein), which are key targets of currently available vaccines. https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html

In vitro studies comparing sera of neutralizing antibody titers from participants in vaccine studies describe use of sera from BNT162b2 SARS-CoV-2 vaccine showing no reduction in neutralization of pseudoviruses bearing the B.1.1.7 variant (ie, UK variant) and the B.1.351 variant (ie, South African variant)

https://www.thermofisher.com/blog/behindthebench/solutions-for-surveillance-of-the-s-gene-mutation-in-the-b117-501yv1-sars-cov-2-strain-lineage/?cid=gsd_cbu_sbu_r07_co_cp1422_pjt6968_gsd00000_0se_gaw_ta_lgn_em-b117-sars&gclid=Cj0KCQiA0-6ABhDMARIsAFVdQv-gyoVZcaZSIDCCgoO4WYGhA5gU2sLZaIcrVgLlFqbLheUUpqllK48aAqzQEALw_wcB

Similarly, the mRNA-1273 vaccine neutralizing capabilities were assessed against these variants. No significant impact on neutralization against the B.1.1.7 variant was detected in either case. A reduced, but still significant neutralization was measured against the mutations present in B.1.351 (**Kai Wu, Anne P Werner, Juan I Moliva, Matthew Koch, Angela Choi, Guillaume B E Stewart-Jones, Hamilton Bennett, Seyhan Boyoglu-Barnum, Wei Shi, Barney S Graham, Andrea Carfi, Kizzmekia S Corbett, Robert A Seder, Darin K EdwardsmRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variantsbioRxiv . 2021 Jan 25;2021.01.25.427948. doi: 10.1101/2021.01.25.427948**.)
A slight decreased neutralization is not considered to be clinically significant regarding vaccine efficacy, owing to the very high efficacy of each mRNA vaccine (ie, approximately 95%). Continued variant surveillance will allow foresight for any needed changes to vaccine development or future booster doses that may be warranted.
Moderna announced its clinical strategy to proactively address the pandemic as the virus continues to evolve. The company will test an additional booster dose (ie, third dos) of its mRNA-1273 vaccine to study the ability to further increase neutralizing titers against emerging strains beyond the existing primary vaccination series. Additionally, the company is advancing mRNA-1273.351 into preclinical studies and a Phase 1 study in the United States to evaluate the immunological benefit of boosting with strain-specific spike proteins. https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-primary-efficacy-analysis-phase-3-cove-study/

Novavax reported preliminary efficacy results for NVX-CoV2373 vaccine from the phase 3 trial in the UK (n > 15,000). Estimated vaccine efficacy was 89.3%. The UK variant was detected in over 50% of PCR-confirmed symptomatic cases (32 UK variant, 24 nonvariant, 6 unknown). The

calculated efficacy was 85.6% for the UK strain and 95.6% for the original strain. https://www.who.int/news-room/q-a-detail/vaccines-and-immunization-what-is-vaccination?adgroupsurvey={adgroupsurvey}&gclid=Cj0KCQiA0-6ABhDMARIsAFVdQv_RjQRO6OagA9_aNSRdCdnIJTsgSMKxLqHivJvVD1zMF92_eU3_3BcaAv4gEALw_wcB

Preliminary data from the Phase 2b trial (n > 4,400) conducted in South Africa for NVX-CoV2373 reported 60% efficacy in the 94% of the study population that was HIV-negative. Among the 44 individuals testing positive for COVID-19, the South African escape variant was detected in 92.6% cases analyzed (25 out of 27 cases).

Johnson & Johnson reported phase 3 trial results (EMSEMBLE; n= 43,783) for their single-dose Ad26.COV2.S viral vector vaccine in late January 2021. The trial was conducted in geographical regions and during the time when several variants emerged. At Day 28, the vaccine was 72% effective in the US, 66% in Latin America, and 57% in South Africa at preventing moderate-to-severe COVID-19 infection. Importantly, the vaccine was 85% effective in preventing severe disease and provided complete protection against COVID-related hospitalization and death in all geographic regions. Additionally, it showed consistent protection across all variants and regions studied, including South Africa where nearly all cases of COVID-19 (95%) were due to infection with a SARS-CoV-2 variant from the B.1.351 lineage https://www.thermofisher.com/blog/behindthebench/solutions-for-surveillance-of-the-s-gene-mutation-in-the-b117-501yv1-sars-cov-2-strain-lineage/?cid=gsd_cbu_sbu_r07_co_cp1422_pjt6968_gsd00000_0se_gaw_ta_lgn_em-b1117-sars&gclid=Cj0KCQiA0-6ABhDMARIsAFVdQv99l5NjN3eZAWEx_hUYQwg6ofGAXT-cWh-ivpCc2l7H1ThVsFTmr60aAh8iEALw_wcB

Other Investigational Vaccines

Additional vaccine candidates are in various stages of development and clinical testing. Examples of these vaccines are provided in

Table . Other Investigational Vaccines

Vaccine	Comments
INO-4800 (Inovio Pharmaceuticals) https://www.inovio.com/our-focus-serving-patients/covid-19/ DNA-based, 2-dose vaccine	Stable at room temperature for more than 1 y; frozen shipment not needed; interim results from phase 1 human trial (n = 40): favorable safety and immunogenicity; expanded to include older participants. Phase 2/3 trial (INNOVATE) ongoing; phase 2 to evaluate 2-dose regimen (1 mg or 2 mg) vs placebo in 400 participants. Grant from Bill and Melinda Gates Foundation to speed testing and scale up a smart device (Cellectra 3PSP) for large-scale intradermal vaccine delivery; company has also received funds from the US Department of Defense.

CVnCoV (CureVac and Bayer) https://media.bayer.com/baynews/baynews.nsf/id/CureVac-and-Bayer-join-forces-on-COVID-19-vaccine-candidate-CVnCoV https://media.bayer.com/baynews/baynews.nsf/id/CureVac-and-Bayer-join-forces-on-COVID-19-vaccine-candidate-CVnCoV mRNA, 2-dose vaccine	Preliminary data from phase 1 dose-escalating trial: 12-µg dose provided IgG antibody levels similar to convalescent plasma. Phase 2b/3 trial enrollment (goal, 35,000 in Europe and Latin America) ongoing.
COVID-19 S-Trimer (GlaxoSmithKline [GSK]) https://www.reuters.com/article/health-coronavirus-clover-gsk/chinas-clover-ends-covid-19-vaccine-partnership-with-gsk-idUSL1N2K70OA	Partnering with multiple companies using GSK's adjuvants (compounds that enhance vaccine efficacy).
CpG 1018 adjuvant vaccine (Dynavax) https://www.creative-biolabs.com/vaccine/1-cpG-21.htm?gclid=Cj0KCQiA0-6ABhDMARIsAFVdQv9ir8Z71cdTZDgP_ei1tSV5Ax0x-APnh3vMLs0_MsCgqtY2G-o6o_kaAqJnEALw_wcB	Under development with Sanofi's S-protein COVID-19 antigen and GSK's adjuvant technology that stimulates the immune system; phase 1/2 trial ongoing.

UB-612 multitope peptide-based vaccine (COVAXX [division of United Biomedical, Inc]) https://www.difficultpeptide.com/custom-peptide-synthesis_c1?gclid=Cj0KCQiA0-6ABhDMARIsAFVdQv8ty2BACFvHNWAvJigpYrMPhOncZI0OCm5FGckJ9aFbAYSRf35AJFMaAhb5EALw_wcB	Comprises SARS-CoV-2 amino acid sequences of the receptor binding domain; further formulated with designer Th and CTL epitope peptides derived from the S2 subunit, membrane, and nucleoprotein regions of SARS-CoV-2 structural proteins for induction of memory recall, T-cell activation, and effector functions against SARS-CoV-2. Company partnering with University of Nebraska Medical Center in the United States; phase 1, open-label, dose escalation study ongoing in Taiwan.

HaloVax (Hoth Therapeutics; Voltron Therapeutics) https://hoththerapeutics.com/pipeline/halo-vax/	Collaboration with the Vaccine and Immunotherapy Center at Massachusetts General Hospital; use of VaxCelerate self-assembling vaccine platform offers 1 fixed immune adjuvant and 1 variable immune target to allow rapid development.
Nanoparticle SARS-CoV-2 vaccine (Ufovax) [32]	Vaccine prototype development utilizing self-assembling protein nanoparticle (1c-SapNP) vaccine platform technology.
PDA0203 (PDS Biotechnology Corp) https://www.pdsbiotech.com/	Utilizes Versamune T-cell-activating platform for vaccine development.

CoVLP recombinant coronavirus virus-like particles (Medicago and GlaxoSmithKline)	Combines Medicago's recombinant coronavirus virus-like particles (rCoVLP) with GSK's adjuvant system; phase 2/3 trial ongoing.
Covaxin (Bharat Biotech and Ocugen) Whole-virion inactivated vaccine https://www.great.gov.uk/international/content/about-uk/industries/health-and-life-sciences/?utm_campaign=rtt&utm_source=google&utm_medium=paidsearch&utm_content=rttq4-paidsearch-lifesciences&gclid=Cj0KCQiA0-6ABhDMARIsAFVdQv-sBSnxFnk1mduQzy3sALtxr2PpbmM0VVDMV_Hhj2yLGaCt3xVlNLQaAgqiEALw_wcB&gclsrc=aw.ds	Developed and manufactured in Bharat Biotech's bio-safety level 3 biocontainment facility. Co-development with Ocugen announced for the US market. Elicited strong IgG responses against spike (S1) protein, receptor-binding domain (RBD) and the nucleocapsid (N) protein of SARS-CoV-2 along with strong cellular responses in Phase 1 and 2 clinical trials (n ~1000). Phase 3 trial is in progress in India that involves 26,000 volunteers.

Recombinant adenovirus type-5-vectored vaccine (Ad5-vectored vaccine; Sinopharm [China]) https://viraquest.com/products/?gclid=Cj0KCQiA0-6ABhDMARIsAFVdQv8CXslLVptMyBPjx5tTH-T_elrDmd5FighHmdPFY5QHruIOQnixguAaAl4SEALw_wcB	Approved in China and Saudi Arabia; preliminary data: 86% efficacy; phase 2 trial: seroconversion of neutralizing antibodies seen in 59% and 47% of those in 2-dose groups; seroconversion of binding antibody seen in 96-97% of participants; Positive specific T-cell responses seen in 88-90% of participants.
CoronaVac (Ad5-vectored vaccine; Sinovac [China]) https://www.nature.com/npjvaccines/?gclid=Cj0KCQiA0-6ABhDMARIsAFVdQv8RsBr6Kadu0J8TMaXZUcKOm-5S5Cho-oSgIBLm8r8sC55Z4mEVXg0aAurjEALw_wcB	Limited use in China. Interim phase 3 efficacy reports vary widely from several trials. A trial in Brazil reports efficacy of 50-90%. However, a Turkish trial reports 91.25% efficacy (n = 7,371; data analysis based on 1322 participants – 752 vaccine and 570 placebo).

rAd26 (frozen) and rAd5 vector-based (lyophilized) formulations (Sputnik V; Moscow Gamaleya Institute) https://www.sigmaaldrich.com/catalog/search?term=9025-65-4&interface=CAS%20No.&N=0&mode=partialmax&lang=pt&region=BR&focus=product&gclid=Cj0KCQiA0-6ABhDMARIsAFVdQv_2PeiMF-PeVcWFQUXELPQ2-IFUWvNe8uoIczdHE7jB5FhoXDdP740aAv7cEALw_wcB	Approved in Russia. Each vaccine vector carries gene for full-length SARS-CoV-2 glycoprotein S. The phase 3 trial administered 2 doses 21 days apart (rAd26 then rAd5) assigned in a 3:1 ratio of vaccine (n = 16,501) or placebo (n = 5,476). Interim analysis of results 21-days after the first dose (ie, day of dose 2) showed confirm COVID-19 infection in 0.1% of the vaccine group compared with 1.3% of the placebo group translating to 91.3% efficacy.

hAd5 -COVID-19 (ImmunityBio) https://www.raadfest.com/raad-fest//ageless-immune-system?gclid=Cj0KCQiA0-6ABhDMARIsAFVdQv_hL-1Ulea3Ng91j7iUjmmVmFfk25r24B7Ucj8A1NoAL3VbQKb021IaAhrxEALw_wcB	Phase 1 trial ongoing; vaccine targets inner nucleocapsid (N) and outer spike (S) protein, which have been engineered to activate T cells and antibodies against SARS-CoV-2, respectively. These dual constructs offer the possibility for the vaccine candidate to provide durable, long-term cell-mediated immunity with potent antibody stimulation to patients against both the S and N proteins.

MRT5500 (Sanofi and Translate Bio) https://www.who.int/news-room/q-a-detail/vaccines-and-immunization-what-is-vaccination?adgroupsurvey={adgroupsurvey}&gclid=Cj0KCQiA0-6ABhDMARIsAFVdQv8biDjOsXJpTBTjDJfAKkkSOD791nzsHXBFlMASHNMmnwzsMFvMasMaAo1XEALw_wcB	mRNA-based vaccine candidate; preclinical evaluation demonstrated favorable ability to elicit neutralizing antibodies using a 2-dose schedule administered 3 wk apart; phase 1/2 trial anticipated to start in Q4 2020.
AG0302-COVID19 (AnGes and Brickell Biotech)	Adjuvanted DNA vaccine https://www.precisionvaccinations.com/vaccines/ag0301-covid-19-vaccine in phase 1/2 study in Japan; data readouts expected in Q1 2021; intent to follow with phase 3 trials in United States and South America.
EPV-CoV-19 (EpiVax)	Subunit, T-cell epitope-directed vaccine. Preclinical validation studies completed. Clinical trial anticipated in early 2021.

Discontiniued vaccine development Vaccine candidates V590 and V591 (Merck) [42]	V590 and V591 (subunit vaccines): Phase 1 studies showed immune responses were inferior to natural infection and those reported for other SARS-CoV-2 vaccines.

Noninjectable Investigational Vaccines
Routes of vaccine administration other than injection are also undergoing development.

Noninjectable Vaccine	Comments
Intranasal COVID-19 vaccine (AdCOVID; Altimmune, Inc)	Single-dose vaccine; preclinical results completed at University of Alabama Birmingham showed stimulation of antigen-specific CD4+ and CD8+ T-cells in mildly affected lungs as early as 10 d; phase 1 safety and immunogenicity study expected to begin in Q4 2020.
ChAdOx1 nCov-19 inhaled (University of Oxford)	Dose-ranging trial for orally inhaled vaccine beginning phase 1 trials in 30 volunteers in Fall 2020.

saRNA inhaled (Imperial College of London)	Dose-ranging trial for orally inhaled vaccine beginning phase 1 trials in 30 volunteers in Fall 2020.
VXA-CoV2-1 oral vaccine (Vaxart)	Recombinant adenovirus vector type 5 (Ad5) expressing coronavirus antigen and a toll-like receptor 3 (TLR3) agonist as an adjuvant. Preliminary phase 1 trial (n = 495) showed induced CD8 T-cell responses to the viral spike protein. Neutralizing antibodies not detected in most subjects. Company is evaluating optimal dosing schedule in order to assess efficacy in phase 2 trials.
PittCoVacc (University of Pittsburgh School of Medicine)	Vaccine candidate using transdermal microneedle for COVID-19; testing in mice produced antibodies over a 2-wk period; microneedles are made of sugar, making it easy to mass-produce and store without refrigeration.