Synthesis Summary

COVID-19 Vaccines

March 5, 2021

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Within one year of the first identification of SARS-CoV-2, several vaccines were unequivocally demonstrated to prevent clinical COVID-19. This document is **a brief summary of the published evidence to date regarding the safety and efficacy of vaccines to prevent COVID-19 with a primary focus on the results of clinical trials.** The document is not specifically intended to inform decisions regarding prioritization of specific populations, the cost-effectiveness of specific vaccination approaches, or other logistics surrounding vaccine implementation. For additional information regarding how emerging SARS-CoV-2 variants potentially affect vaccine efficacy, please consult the variants report. References summarized in this report were drawn from the daily COVID-19 Literature Situation Report.

Executive Summary of SARS-CoV-2 Vaccine Trials

- **COVID-19 is a vaccine preventable illness.**
- **All vaccine candidates reported to date have demonstrated a very high degree of efficacy against hospitalization and death from COVID-19.**
- **Vaccines have reported variable efficacy against mild-to-moderate disease. Direct comparison across different trials is hampered by different definitions of "mild," "moderate," and "severe" disease. The emergence of variant viruses further complicates direct cross-trial comparison.**
- **The most serious safety signal observed to date is anaphylaxis in response to the mRNA vaccines, which occurs at a rate of one episode per 11.1 per million doses (Pfizer-BioNTech) and one episode per 2.5 per million doses (Moderna). No deaths attributable to any vaccine have been reported to date.**

Overview of Vaccine Efficacy Trials

Within 9 months of the first description of SARS-CoV-2 associated respiratory disease in Wuhan, efficacy trials established unequivocally that COVID-19 is a vaccine-preventable disease. The rapid development schedule has prompted questions regarding the mechanism for rapid approval of vaccines for COVID-19 and whether safety or data quality have been compromised. For reference, the shortest development cycle under modern approval mechanisms was ~5 years for Ebola, and a typical vaccine approval cycle takes 10-15 years (Wolf). Time savings over traditional vaccine development strategies largely was

achieved with the following strategies: (1) immediately starting efficacy trials after establishing that vaccines were safe and immunogenic (rather than waiting for information regarding the durability of the immune response); (2) the large size of the populations enrolled; and (3) a "time-to-analysis" trial design whereby pre-specified interim reviews were based upon a specific number of observed infections (rather than a predefined observation period). The allocation of unprecedented resources on an international scale also undoubtedly increased the pace of development.

The current regulatory landscape is rapidly evolving and as of March 5, 2021, three vaccines have achieved **emergency use authorization (EUA)** in the United States:

- BNT162b2 from **Pfizer-BioNTech** (2 doses)**,**
- mRNA-1273 from **Moderna** (2 doses)
- Ad26.COV2.S from **Johnson & Johnson-Janssen** (1 dose)

At least 13 million people have received EUA-approved vaccines to date with an acceptable safety profile (Gee). Another candidate vaccine currently undergoing phase III trials to support licensure in the United States is from **Novovax** (a two-dose regimen). Some sponsors also undertook additional trials that were conducted in parallel to the US trials to support licensure in other countries. For example, there is an ongoing trial of the **University of Oxford-AztraZeneca** product intended to support licensure in the United States whereas this product has already been approved by the UK and other international regulators on the basis of trials conducted in these countries. Other vaccines have achieved international licensure and are not, to date, conducting trials to support licensure in the United States. These include products from Sinovac in China (**Coronavac**) and **Gamaleya** Research Institute in Russia (**Sputnik V**). All vaccines to date target the spike protein of the SARS-CoV-2 virus, but use a variety of platforms to deliver the spike antigen, including mRNA (**Pfizer-BioNTech** and **Moderna**), replication incompetent viruses (**Oxford-AstraZeneca**, **Johnson & Johnson-Janssen, Gamaleya-Sputnik V**), recombinant proteins (**Novovax**), and inactivated virus (**Coronavac**). There are at least 50 candidate vaccines in various stages of early clinical testing using a variety of approaches; the specific details of these products are beyond the scope of this review.

All trials thus far are randomized, placebo-controlled trials with laboratory confirmed SARS-CoV-2 infection combined with COVID-19 disease considered to be the primary endpoint. It is important to note that there are differences in how each trial has defined clinical disease, specifically with respect to the "mild", "moderate" and "severe" categories. Furthermore, there are minor differences in the populations enrolled and the time period in which the trials were conducted, making direct cross protocol comparison complex. The pre-specified statistical analysis plan of each trial to date conducted in the US included a minimum number of clinical endpoints (e.g., PCR-confirmed SARS-CoV-2 infection plus clinical signs or symptoms defining mild, moderate, or severe COVID-19) that triggered an interim analysis (typically around 100-150 cases). The definitions of the primary endpoints used in each trial are outline below the sections describing each vaccine. In general, the protocols were designed assuming a much lower rate of community transmission than was actually observed (an assumption of ~1% of placebo recipients per year becoming infected versus an observed rate of ~5-10% per year); the high rate of community transmission, therefore, contributed to the rapid pace of determining whether a vaccine was effective because of the "case-based" design of the trials.

Safety Monitoring

Although it is somewhat counter-intuitive given the rapid pace of vaccine approval, the COVID-19 vaccine trials have generated **substantially more short-term safety data than would be available during a typical vaccine approval process**. For example, each of the efficacy trials intended for licensure in the United States have enrolled (or plan to enroll) >30,000 participants, with between 15,000 and 20,000 administered study product. For comparison, the RESOLVE trial, which was intended to support licensure of a vaccine against lower respiratory tract infection caused by respiratory syncytial virus (RSV) only enrolled 11,856 participants with 1:1 randomization, meaning only 5,921 participants were administered study product (https://clinicaltrials.gov/ct2/show/NCT02608502). Additionally, the generally consistent vaccination strategy between products (e.g., using similar inserts of the spike protein of the SARS-CoV-2 virus) offers an unprecedented capacity for comparing the safety profile and performance across various platforms. The fact that multiple trials were conducted in parallel allows for a **high degree of confidence that targeting the spike protein via a variety of vaccination strategies is both safe and effective**. An important technical note is the conceptual differentiation in safety outcomes between **reactogenicity (e.g., transient symptoms such as malaise, for example)** and **serious adverse events attributable to the vaccine (e.g., Guillain-Barre syndrome, anaphylaxis)**. The former is quite common with all vaccines, whereas the latter are extremely rare. The CDC is aggressively monitoring vaccines implemented using an EUA with a post-marketing surveillance program.

Notable safety findings:

- Both mRNA vaccines currently authorized for use in the US under an EUA (Pfizer-BioNTech and Moderna) have been associated with low rates of anaphylaxis in post-marketing surveillance (Shimabukuro)
- Symptoms consistent with "reactogenicity" occurring soon after vaccination have been frequent but transient (Baden, Gee)
- Delayed late local reactions at the injection site (erythema, swelling, pain) have been reported to occur with the Moderna vaccine at a rate of 0.5-1% (Baden). Such reactions have been less frequently reported with the Pfizer vaccine. If these delayed injection site reactions occur with the first dose, the CDC states that they are not a contraindication for a second dose of the vaccine (CDC).

Summaries of relevant articles:

Gee et al. (Feb 19, 2021). First Month of COVID-19 Vaccine Safety Monitoring — United States, December 14, 2020–January 13, 2021. MMWR. Morbidity and Mortality Weekly Report. https://doi.org/10.15585/mmwr.mm7008e3

- Both the Moderna and Pfizer vaccines had an acceptable safety profile, according to an analysis of the Vaccine Adverse Event Reporting System (VAERS). A total of 13,794,904 COVID-19 vaccine doses were administered in the U.S from December 14, 2020 to January 13. There were 6,994 reports of COVID-19–associated adverse events to VAERS during the period, with 91% of these events classified as non-serious.
- VAERS received 113 reports of death after COVID-19 vaccinations. Two thirds of these deaths were among residents of long-term care facilities and a review did not indicate an unexpected pattern that might suggest a causal relationship with vaccination. There were 35 reports of deaths in people

not in long-term care facilities. For the 16 reported deaths where records were reviewed, death certificates or other data indicated underlying heart disease, cancer, stroke, probable pulmonary embolism, and otherwise frail health as the cause of death.

Shimabukuro et al. (Feb 12, 2021). Reports of Anaphylaxis After Receipt of MRNA COVID-19 Vaccines in the US—December 14, 2020-January 18, 2021. JAMA. https://doi.org/10.1001/jama.2021.1967

- The CDC identified 66 reports of anaphylaxis from the Vaccine Adverse Event Reporting System (VAERS) during December 14, 2020 to January 18, 2021 (47 cases out of nearly 10 million Pfizer vaccine doses and 19 cases out of nearly 7.6 million Moderna vaccine doses). All cases were treated in healthcare settings, and no deaths from anaphylaxis after vaccination with either vaccine were reported. CDC physician reviewers concluded that the clinical characteristics of anaphylaxis cases following both vaccines were similar. 32% (22 of 66) of case reports noted prior episodes of anaphylaxis from other exposures, including other vaccines, drugs, or food. *[EDITORIAL NOTE: This article includes updated results of analyses summarized in the Lit Rep on January 2 and January 22, 2021.]*

Durability of Vaccine Efficacy

The durability of clinical immunity generated by the various vaccines is currently unknowable given that the epidemic is only a year old, so major questions remain regarding the potential need for booster vaccinations. Evidence regarding the durability of vaccine-induced immunity will be added here has it becomes available.

Impact of Vaccinations on COVID-19 Disease and Community Transmission

Evidence is still emerging regarding the effect that widespread vaccination can have on community transmission of SARS-CoV-2, incidence of COVID-19 cases, and rates of hospitalization and death due to COVID-19. In most settings where vaccination efforts have started, the proportion of the population that has been fully vaccinated is low and therefore the impact of widespread vaccination cannot yet be assessed. However, a small number of countries have vaccinated a large proportion of their population, most notably Israel and the UK. In Israel, where 2-dose vaccination coverage with the Pfizer-BioNTech mRNA vaccine reached 84% among persons aged ≥70 years and 10% among those aged <50 years by February 2021, there was a 67% decline in the ratio of COVID-19 patients aged ≥70 years requiring mechanical ventilation to those aged <50 years (Rinott). The authors conclude that this is preliminary evidence of the effectiveness of vaccines in preventing severe cases of COVID-19 at the national level. Other evidence from Israel indicates that a single dose of the Pfizer-BioNTech vaccine reduced the rate of SARS-CoV-2 infections among health care workers at 15-28 days after the first dose (Amit). Similarly, early evidence from Scotland indicates that under real-world conditions, with approximately 35% of the population vaccinated, there was a peak vaccine efficacy of 85% (95% CI: 76-91%) to prevent COVID-19-related hospitalization following a first dose of for the Pfizer-BioNTech vaccine and 94% (95%CI: 73-99%) efficacy for the Oxford-AstraZeneca vaccine, with the peak occurring at 28-34 days post-vaccination (Vasileiou).

Summaries of relevant articles:

Vasileiou et al. (Feb 19, 2021). Effectiveness of First Dose of COVID-19 Vaccines against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 Million People. Pre-print downloaded Feb 23 from https://ssrn.com/abstract=3789264

- *[Pre-print, not peer-reviewed]* A national prospective cohort study including approximately 99% of residents in Scotland (n=5.4 million) found a peak vaccine efficacy to prevent COVID-19-related hospitalization following a first dose of 85% (95% CI: 76-91%) for the Pfizer vaccine and 94% (95%CI: 73-99%) for the Oxford-AstraZeneca vaccine, with the peak occurring at 28-34 days post-vaccination. Approximately 35% of the study cohort was vaccinated. Restricting that analysis to those aged 80 or older resulted in an efficacy of 81% at 28-34 days post-vaccination. Vaccine efficacy in preventing hospitalization declined to 58% at 48 or more days post-vaccination, with the largest decline among those aged 18-64 years.

Pawlowski et al. (Feb 18, 2021). FDA-Authorized COVID-19 Vaccines Are Effective per Real-World Evidence Synthesized across a Multi-State Health System. Pre-print downloaded Feb 18 from https://doi.org/10.1101/2021.02.15.21251623

- *[Pre-print, not peer reviewed]* The Moderna and Pfizer vaccines were 89% effective (95% CI: 68-97%) in preventing SARS-CoV-2 infection occurring at least 36 days after the first dose in a 1:1 propensity score matched analysis of over 60,000 individuals in the US between December 2020 to February 2021. Among those subsequently diagnosed with COVID-19, vaccinated patients had significantly lower 14-day hospital admission rates compared to matched unvaccinated counterparts (3.7% vs 9.2%). Vaccine efficacy 7 days after receiving the first dose was 54% (95% CI: 41-64%), which increased over time to a maximum of 93% (95% CI: 70-99%) between days 36-42.
- The authors note that a key limitation of the study was shorter follow-up time compared to the phase 3 trials (27 days vs. 80-90 days); 45% of the vaccinated cohort had only received one vaccine dose for some efficacy analyses. Additionally, bias on seeking PCR testing between vaccinated and unvaccinated patients was not addressed.

Abu Jabal et al. (Feb 11, 2021). Impact of Age, Ethnicity, Sex and Prior Infection Status on Immunogenicity Following a Single Dose of the BNT162b2 MRNA COVID-19 Vaccine: Real-World Evidence from Healthcare Workers, Israel, December 2020 to January 2021. Eurosurveillance. https://doi.org/10.2807/1560-7917.ES.2021.26.6.2100096

- A single dose of the Pfizer SARS-CoV-2 vaccine produced detectable anti-SARS-CoV-2 spike IgG antibodies 21 days after vaccination in 92% (n=475) of a cohort of healthcare workers in Israel, including in 92% (n=458) of people who had no history of COVID-19 infection. The 39 healthcare workers who did not respond to the first dose were older (mean age 57) than those who did (mean age 45). Among those with antibodies after vaccination, IgG titers decreased with increasing age, although the authors note that the decrease was small and of unclear clinical significance. In people with a history of COVID-19, the single vaccine dose was associated with IgG titres approximately one order of magnitude higher compared with vaccinated individuals with no prior history of COVID-19.

Impact of Viral Evolution on Vaccine Efficacy

While it is incontrovertible that clinical COVID-19 can be prevented by vaccination, there are major outstanding questions about how SARS-CoV-2 evolution in response to immune pressure from both natural and vaccine-induced immunity will affect the efficacy of the current generation of SARS-CoV-2 vaccines. The most direct impact of viral mutations on vaccine efficacy come from countries where variants were circulating at the time of ongoing efficacy trials. The variant of currently of greatest concern regarding vaccine efficacy is the B.1.351 variant (first described in South Africa). There were ongoing trials of the Oxford-AstraZeneca and Johnson & Johnson-Janssen vaccines in South Africa at a time when the B.1.1.351 variant was the dominant circulating strain. For the Oxford-AstraZeneca SARS-CoV-2 vaccine, efficacy against mild or moderate COVID-19 due to infection with the B.1.351 variant was estimated to be 10% (Madhi). The authors were unable to make conclusions about protection from severe COVID-19 since no cases of severe disease or hospitalization were reported in either the vaccinated or placebo group. By contrast, the efficacy of the Johnson & Johnson-Janssen vaccine to protect against severe/critical COVID-19 was equivalent in South Africa (81.7%), where the B.1.351 variants accounted for 95% of infections, compared to other regions where the B.1.351 variant was not circulating (85.9% in the US and 87.6% in Brazil) (FDA). The efficacy of the Johnson & Johnson-Janssen vaccine against moderate COVID-19 was somewhat lower in South Africa compared to the US and Brazil. Vaccine efficacy appears to be similar against the B.1.1.7 variant (first described in the UK) compared to other viral lineages.

Indirect evidence for the effect of viral mutations on vaccine efficacy comes from studies using serum derived from blood samples drawn from individuals who had received one of the COVID-19 vaccines. Across multiple studies, neutralization assays indicate somewhat lower neutralization activity against the B.1.1.7 variant compared to other viral lineages (Xie, Wu, Weisblum). Authors have generally concluded that these modest reductions in neutralization activity are unlikely to result in reduced vaccine efficacy. Considerably larger reductions in neutralizing activity against the B.1.351 variant have been observed (Garcia-Beltran, Liu, Wu, Diamond) and authors have expressed concerns that this could indicate lower vaccine efficacy against B.1.351. However, the relationship between levels of in vitro neutralization and actual vaccine efficacy remains unclear and there is no currently accepted correlate of immunity.

Summaries of relevant articles:

Trial and real world evidence involving variants of concern

Madhi et al. (Feb 12, 2021). Safety and Efficacy of the ChAdOx1 NCoV-19 (AZD1222) Covid-19 Vaccine against the B.1.351 Variant in South Africa. Pre-print downloaded Feb 12 from https://www.medrxiv.org/content/10.1101/2021.02.10.21251247v1

- *[pre-print; not peer-reviewed]* A randomized trial conducted in South Africa found the incidence of COVID-19 >14 days after the second dose of the Oxford-AstraZeneca SARS-CoV-2 vaccine was 93.6 per 1,000 person-years (23 cases among 717 participants) in the vaccine group and 73.1 per 1,000 person-years (19 cases among 750 participants) in the placebo group, yielding a vaccine efficacy of 22%. Of the COVID-19 cases, 39/42 (93%) were the B.1.351 variant, corresponding to a vaccine efficacy of 10% against this variant. Although the researchers conclude that the vaccine does not provide protection from mild to moderate infection caused by the B.1.351 variant, they were unable

to make conclusions about protection from severe COVID-19 since no cases of severe disease or hospitalization were reported in either the vaccinated or placebo group.
- Analysis of serum samples collected from 25 vaccinated participants demonstrated that the vaccine did not induce neutralization activity against the B.1.351 variant.

***In vitro* evidence**

Garcia-Beltran et al. (Feb 18, 2021). Circulating SARS-CoV-2 Variants Escape Neutralization by Vaccine-Induced Humoral Immunity. Pre-print downloaded Feb 18 from https://doi.org/10.1101/2021.02.14.21251704

- *[Pre-print, not peer reviewed]* Analysis of neutralizing activity of sera from individuals vaccinated with either 1 or 2 doses of the Moderna or Pfizer vaccines (n=48) against SARS-CoV-2 pseudoviruses bearing spike proteins with the partial or full set of mutations from the B.1.351 variant show up to a 97-fold decrease in neutralization compared to wild-type. Notably, neutralization of B.1351 was not detectable in samples from 36% (8/22) recipients of 2-dose Pfizer vaccine and 50% (2/4) recipients of 2-dose Moderna vaccine. In contrast, other variants such as the D614G variant, the B.1.1.7 variant, and variants from the P.1 lineage had relatively lower reductions in neutralization.
- Assays conducted with sera from 22 of the 2-dose Pfizer vaccine recipients show that neutralization of B.1.351 in the absence of the mutations present in the receptor binding domain (RBD) was comparable to that of D614G, suggesting that the RBD mutations of the B.1.351 variant are key to neutralization resistance.

Liu et al. (Feb 17, 2021). Neutralizing Activity of BNT162b2-Elicited Serum — Preliminary Report. New England Journal of Medicine. https://doi.org/10.1056/NEJMc2102017

- Neutralizing activity of sera from recipients of the 2-dose Pfizer vaccine (n=15, 20 serum samples) against wild-type SARS-CoV-2 (USA-WA1/2020) engineered with the full set of spike protein mutations of the B.1.351 variant was weaker than the USA-WA1/2020 strain by approximately two-thirds. Using 50% plaque reduction neutralization testing (PRNT50) on sera obtained 2-4 weeks after the second dose, geometric mean titers against USA-WA1/2020, USA-WA1/2020 with the globally dominant D614G mutation, USA-WA1/2020 with key B.1.351 mutations (K417N, E484K, and N501Y), and USA-WA1/2020 with the full set of B.1.351 mutations were 501, 485, 331, and 184, respectively.

Wu et al. (Feb 17, 2021). Serum Neutralizing Activity Elicited by MRNA-1273 Vaccine — Preliminary Report. New England Journal of Medicine. https://doi.org/10.1056/NEJMc2102179

- Neutralizing activity of sera from recipients of the 2-dose Moderna vaccine in the phase 1 trial (n=45) were similar against a SARS-CoV-2 pseudovirus bearing the spike protein from the original Wuhan-Hu-1 isolate, the D614G variant, as well as against 20E (EU1), 20A.EU2, N439K-D614G, and mink cluster 5 variants. In contrast, neutralizing titers against the D614G variant decreased 2.7-fold against a pseudovirus with a partial set of the mutations in the B.1.351 variant (mutations K417N, E484K, and N501Y), and by 6.4-fold against the full set of B.1.351 mutations. Sera obtained from 8 participants still neutralized the B.1.351 variant at low dilutions. *[EDITORIAL NOTE: This article was summarized as a pre-print on January 25, 2021.]*

Diamond et al. (Feb 2021). SARS-CoV-2 Variants Show Resistance to Neutralization by Many Monoclonal and Serum-Derived Polyclonal Antibodies. Research Square. https://doi.org/10.21203/rs.3.rs-228079/v1

- *[Pre-print, not peer-reviewed]* Most convalescent sera from people who had recovered from COVID-19 and virtually all Pfizer-BioNTech mRNA vaccine-induced immune sera were shown to have diminished neutralizing activity against engineered SARS-CoV-2 strains including a chimeric strain combining a strain identified in Washington state with a B.1.351 spike gene (Wash SA-B.1.351 strain), or recombinant viruses containing mutations at position 484 and 501. Several highly neutralizing monoclonal antibodies (mAbs) lost inhibitory activity against Wash SA-B.1.351 or recombinant variants with an E484K spike mutation. The authors note that targeting of highly conserved regions, enhancement of mAb potency, or adjustments to the spike sequences of vaccines may be needed to prevent loss of protection *in vivo*.

Xie et al. (Jan 7, 2021). Neutralization of N501Y Mutant SARS-CoV-2 by BNT162b2 Vaccine-Elicited Sera. Pre-print downloaded Jan 8 from https://www.biorxiv.org/content/10.1101/2021.01.07.425740v1

- *pre-print, not peer-reviewed]* Sera from people vaccinated with the Pfizer-BioNTech mRNA vaccine (BNT162b2) (n=20) had equivalent neutralizing antibody titers to the SARS-CoV-2 strain on which the vaccine was based and a laboratory-developed SARS-CoV-2 strain carrying a N501Y substitution, which is one of the mutations associated with rapidly spreading variants in the United Kingdom and South Africa. The ratio of the 50% neutralization geometric mean titers of the sera against the Y501 virus to that against the N501 virus was 1.46, indicating no reduction in neutralization activity against the virus bearing the Y501 spike. The authors caution that the Y501 virus tested does not include all of the mutations in the spike protein that are found on the rapidly spreading strains in the UK and South Africa.

Vaccines Currently Authorized for Use in the US

The evidence presented below represent publicly available information either released by companies or published in peer-reviewed literature. Additional information has certainly accrued since these data were made available and are likely available to regulators such as the FDA. All trials use PCR to confirm active SARS-CoV-2 infection and have used various clinical definitions for the primary outcomes measured for each trial.

Moderna Vaccine

Type: mRNA
Doses: 2 doses 28 days apart
Handling requirements: (per EUA package insert) Store -25 °C to -15 °C. Can be refrigerated up to 30 days at 2 °C to 8 °C prior to use (cannot refreeze).
Level of evidence for efficacy: Phase III placebo-controlled efficacy trial
Regulatory status:

US: Approved for use under an Emergency Use Authorization

- Results from a phase 3 randomized, observer-blinded, placebo-controlled trial of the Moderna SARS-CoV-2 vaccine candidate (mRNA-1273) indicated that the vaccine showed 94.1% efficacy at preventing COVID-19, including severe disease. 30,420 volunteers were enrolled (15,210 placebo, 15,210 vaccine).
- Efficacy was similar across key secondary analyses, including in participants who had evidence of SARS-CoV-2 infection at baseline and analyses in participants 65 years of age or older.
- Serious adverse events were rare, and the incidence was similar to placebo.
- Reactogenicity after one dose was less than that observed for the recombinant adjuvanted herpes zoster (shingles) vaccine and after the second mRNA-1273 dose was similar to that of the herpes zoster vaccine (Cunningham).

Primary Endpoints by arm

Group	***Total enrolled***	***Any COVID-19***	***Mild COVID-19***	***Severe COVID-19***
Placebo	*15,210*	*185*	*155*	*30*
Vaccine	*15,210*	*11*	*11*	*0*

Definition of primary endpoints

PCR+ with approved test PLUS:

Mild COVID-19	**Moderate COVID-19**	**Severe COVID-19**
Any fever **OR** >48 hours of any of the following: • Shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours) • Cough (of any duration, including ≤ 48 hours) • Fatigue	Not defined	Any of the following: • Respiratory rate >30 breaths/minute • Heart rate >125 beats per minutes • Blood oxygen (SpO_2) less than 93% • Respiratory failure or acute respiratory distress syndrome (ARDS) • Shock • Acute renal, hepatic, or neurologic dysfunction

• Muscle or body aches • Headache • New loss of taste or smell • Sore throat • Congestion or runny nose • Nausea or vomiting • Diarrhea		• ICU admission or death

Summaries of relevant articles:

Baden et al. (Dec 30, 2020). Efficacy and Safety of the MRNA-1273 SARS-CoV-2 Vaccine. New England Journal of Medicine. https://doi.org/10.1056/NEJMoa2035389

- Results from a phase 3 randomized, observer-blinded, placebo-controlled trial of the Moderna SARS-CoV-2 vaccine candidate (mRNA-1273) indicated that the vaccine showed 94.1% efficacy at preventing COVID-19, including severe disease. The trial enrolled 30,420 volunteers, and symptomatic illness was confirmed in 185 participants in the placebo group and in 11 participants in the vaccine group. Efficacy was similar across key secondary analyses, including in participants who had evidence of SARS-CoV-2 infection at baseline and analyses in participants 65 years of age or older. Severe COVID-19 occurred in 30 participants, with one fatality; all 30 were in the placebo group. Serious adverse events were rare, and the incidence was similar in the two groups.

Oliver et al. (Dec 20, 2020). The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Moderna COVID-19 Vaccine — United States, December 2020. MMWR. Morbidity and Mortality Weekly Report. https://doi.org/10.15585/mmwr.mm695152e1

- The Advisory Committee on Immunization Practices issued an interim recommendation for use of the Moderna COVID-19 vaccine in persons aged ≥18 years for the prevention of COVID-19 on December 19, 2020. Vaccination with the Moderna COVID-19 vaccine consists of 2 doses administered intramuscularly 4 weeks apart. Vaccine efficacy after 2 doses was 94.1% in preventing symptomatic, laboratory-confirmed COVID-19 among persons without evidence of previous SARS-CoV-2 infection. Evidence for the vaccine was primarily informed by one large, randomized, double-blind, placebo-controlled Phase III clinical trial that enrolled approximately 30,000 participants.

Pfizer-BioNTech Vaccine

Type: mRNA
Doses: 2 doses, 21 days apart
Handling requirements: -80 °C to -60 °C storage. Once thawed, can store undiluted vials for up to five days (120 hours) at 2C-8C.
Level of evidence for efficacy: Phase III placebo-controlled efficacy trial
Regulatory status:

US: Approved for use under an Emergency Use Authorization

- Results of the phase 3 double-blind, randomized, placebo-controlled trial for the Pfizer-BioNTech mRNA vaccine BNT162b2 (n=21,720 in vaccine group, and 21,728 in placebo group) showed a vaccine efficacy of 95% (95% CI 90.3-97.6), with 8 cases of COVID-19 (1 severe case) in the vaccine group and 162 cases (9 severe cases) in the placebo group.

- Efficacy was similar across subgroups defined by age, sex, race, ethnicity, body-mass index, and presence of co-existing conditions.
- Mild-to-moderate reactogenicity was commonly observed and increased with the second dose. Severe fatigue was observed in approximately 4% of BNT162b2 recipients, which is lower than observed in recipients of the Shingrix vaccine (another approved viral vaccine for older adults).
- Few participants in either group had severe or serious adverse events, and the 6 deaths (2 in vaccine group, 4 in placebo group) were determined by investigators not to be related to the vaccine or placebo by investigators.

Primary Endpoints by arm

Group	***Total enrolled***	***Any COVID-19***	***Mild COVID-19***	***Severe COVID-19***
Placebo	21,728	*162*	*151*	*9*
Vaccine	21,720	*8*	*7*	*1*

Definition of primary endpoints

PCR+ with approved test PLUS:

Mild COVID-19	**Moderate COVID-19**	**Severe COVID-19**
At least one of the following: • Fever, • Cough • Shortness of breath • Chills • Muscle pain • Sore throat • Diarrhea • Vomiting	Not defined	Any of the following: • Respiratory rate >30 breaths/minute • Heart rate >125 beats/minute • shock • acute renal, hepatic or neurologic dysfunction • ICU admission • Death

Summaries of relevant articles:

Polack et al. (Dec 10, 2020). Safety and Efficacy of the BNT162b2 MRNA Covid-19 Vaccine. New England Journal of Medicine. https://doi.org/10.1056/NEJMoa2034577

- Results of the phase 3 double-blind, randomized, placebo-controlled trial for the BioNTech and Pfizer mRNA vaccine BNT162b2 (n=21,720 in vaccine group, and 21,728 in placebo group) showed a vaccine efficacy of 95% (95% CI 90.3-97.6), with 8 cases of COVID-19 (1 severe case) in the vaccine group and 162 cases (9 severe cases) in the placebo group. Efficacy was similar across subgroups defined by age, sex, race, ethnicity, body-mass index, and presence of co-existing conditions.
- Reactogenicity events were common among vaccine recipients, including arm pain, fatigue and headache. Fever (temperature ≥38C) was reported after the second vaccine dose by 16% of participants <55 years old and 11% of participants >55. Few participants in either group had severe or serious adverse events, and the 6 deaths (2 in vaccine group, 4 in placebo group) were determined by investigators not to be related to the vaccine or placebo by investigators.
- Participants were included from 152 sites in 6 countries (130 sites in the US). The majority were aged 18-55 (58%), white (83%), and male (51%). 35% were obese and 21% had at least one coexisting condition.

Oliver et al. (Dec 13, 2020). The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine — United States, December 2020. MMWR. https://doi.org/10.15585/mmwr.mm6950e2

- On Dec 12, 2020, the Advisory Committee on Immunization Practices issued an interim recommendation for use of the Pfizer-BioNTech COVID-19 vaccine in persons in the US aged ≥16 years to prevent COVID-19. Vaccination consists of 2 doses administered intramuscularly 3 weeks apart. The recommendation was primarily informed by findings from a randomized, double-blind, placebo-controlled Phase II/III trial (n = 43,252, median age 52 years) reporting 95% efficacy in preventing symptomatic laboratory-confirmed COVID-19 among persons without previous SARS-CoV-2 infection during a median 2-months of follow-up.

Johnson & Johnson-Janssen Vaccine

Type: Replication incompetent adenovirus (Adenovirus 26)
Doses: 1 dose
Handling requirements: Stored at 2 °C to 8 °C.
Level of evidence for efficacy: Phase III placebo-controlled efficacy trial
Regulatory status:
US: Approved for use under an Emergency Use Authorization

- Vaccine efficacy against laboratory-confirmed moderate to severe/critical COVID-19 across all geographic areas in which the trial was conducted (including South Africa where the B.1.351 variant was circulating at the time) was 66.9% when considering cases occurring at least 14 days after the single-dose vaccination and 66.1% considering cases occurring at least 28 days after vaccination. Efficacy against severe/critical COVID-19 occurring at least 14 days and at least 28 days after vaccination was 76.7% and 85.4%, respectively.

Primary Endpoints (COVID-19 Onset at least 14 Days after vaccination) by arm

		Moderate to severe/critical COVID-19		***Severe/critical COVID-19***	
Group	***Total Enrolled***	***cases***	***Vaccine Efficacy***	***cases***	***Vaccine Efficacy***
Placebo (US)	*9086*	*196*	*74.4%*	*18*	*78.0%*
Vaccine (US)	*9119*	*51*		*4*	
Placebo (South Africa)	*2496*	*90*	*52%*	*30*	*73.1%*
Vaccine (South Africa)	*2473*	*43*		*8*	
Placebo (Brazil)	*3355*	*114*	*66.2%*	*11*	*81.9%*
Vaccine (Brazil)	*3370*	*39*		*2*	

Primary Endpoints (COVID-19 Onset at least 28 Days after vaccination) by arm

		Moderate to severe/critical COVID-19	***Severe/critical COVID-19***

Group	*Total Enrolled*	*cases*	*Vaccine Efficacy*	*cases*	*Vaccine Efficacy*
Placebo (US)	*8835*	*112*	*72.0%*	*7*	*85.9%*
Vaccine (US)	*8958*	*32*		*1*	
Placebo (South Africa)	*2463*	*64*	*64.0%*	*22*	*81.7%*
Vaccine (South Africa)	*2449*	*23*		*4*	
Placebo (Brazil)	*3312*	*74*	*81.7%*	*8*	*87.6%*
Vaccine (Brazil)	*3354*	*24*		*1*	

Definition of primary endpoints

PCR+ with approved test PLUS:

Mild COVID-19	**Moderate COVID-19**	**Severe COVID-19**
One of the following symptoms: • Fever (≥38.0°C or ≥100.4°F), • Sore throat • Malaise (loss of appetite, generally unwell, fatigue, physical weakness) • Headache • Muscle pain (myalgia) • Gastrointestinal symptoms • Cough, • Chest congestion • Runny nose • Wheezing • Skin rash • Eye irritation or discharge • Chills • New or changing olfactory or taste disorders • Red or bruised looking feet or toes • Shaking chills or rigors.	• 3 or more symptoms (see mild COVID-19) **OR** Any one of the following new or worsening signs/symptoms: • Respiratory rate ≥20 breaths/minute • Abnormal SpO_2 but stil >93% on room air at sea level • Clinical or radiologic evidence of pneumonia • Radiologic evidence of deep vein thrombosis • Shortness of breath or difficulty breathing Any 2 of the following new or worsening signs/symptoms • Fever (≥38.0°C or ≥100.4°F) • Heart rate ≥90 beats/minute • Shaking chills or rigors • Sore throat • Cough • Malaise • Headache • Muscle pain (myalgia) • Gastrointestinal symptoms • New or changing olfactory or tase disorder • Red or bruised looking feet or toes	Clinical signs at rest indicative of severe systemic illness: • Respiratory rate ≥30 breaths/minute • Heart rate ≥125 beats/minute • SpO2 ≤93% on room air at sea level, or partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) <300 mmHg) • Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]) • Evidence of shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors) • Significant acute renal, hepatic, or neurologic dysfunction • Admission to the ICU • Death

Summaries of relevant articles:

FDA. (Feb 26, 2021). Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19. Vaccines and Related Biological Products Advisory Committee Meeting. https://www.fda.gov/media/146217/download

- The Johnson & Johnson single-dose Ad26.COV2.S vaccine candidate was determined by the FDA to have met the safety and efficacy requirements for emergency use authorization. Vaccine efficacy against laboratory-confirmed moderate to severe/critical COVID-19 across all geographic areas in which the trial was conducted was 66.9% when considering cases occurring at least 14 days after the single-dose vaccination and 66.1% considering cases occurring at least 28 days after vaccination. Efficacy against severe/critical COVID-19 occurring at least 14 days and at least 28 days after vaccination was 76.7% and 85.4%, respectively. As of February 5, 2021, there were 7 COVID-19 related deaths in the placebo group and no COVID-19 related deaths in the vaccine group. A subset of participants (n=6,736) was followed for self-reported reactions to the vaccine within 7 days following vaccination, and the most common adverse reactions were mild to moderate injection site pain (48.6%), headache (38.9%), fatigue (38.2%), and myalgia (33.2%).

Vaccines Nearing Approval for Use in the US

Novavax Vaccine
Type: Recombinant protein
Doses: 2 doses, 21 days apart
Handling requirements: Store at 2 °C to 8 °C.
Regulatory status:
US: Anticipated EUA application is expected soon on the basis of US trial results

- Based on a press release from Novavax, preliminary results for phase 2/3 trials for the recombinant protein-based COVID-19 vaccine NVX-CoV2373 made by Novavax showed up to **89.3% efficacy in the UK cohort** (n= >15,000), where 56 participants in the placebo group developed COVID-19 vs 6 in the vaccine group (Novavax).
- Of note, the **B.1.1.7 variant** (first described in the UK) was observed in 32 of the COVID-19 cases, yielding an estimate of **85.6% efficacy against the variant**.
- Preliminary results from the **South Africa cohort** (n= >4,400) showed efficacy of **60% in the HIV-negative study population vs. 49.4% in the overall study population**, with 29 COVID-19 cases observed in the placebo group vs. 15 in the vaccine group.
- In the South Africa cohort, among 27 of the 44 cases with sequence data, mutations consistent with the B.1.351 variant (first described in South Africa) were detected in 25 (93%).
- Approximately 1/3 of patients in the South Africa cohort (but not included in the preliminary results) were SARS-CoV-2 seropositive at baseline, indicating prior SARS-CoV-2 infection.

Primary Endpoints by arm (Note: US trial is ongoing)

Group	***Total enrolled***	***Any COVID-19***	***Mild COVID-19***	***Severe COVID-19***
Placebo (UK)	*Approx. half of "15000"*	*56*	*61*	*1*
Vaccine (UK)	*Approx. half of "15000"*	*6*	*6*	*0*
Placebo (South Africa)	*Approx. half of "Over 4400"*	*29*	*29*	*0*
Vaccine (South Africa)	*Approx. half of "Over 4400"*	*15*	*14*	*1*

Definition of primary endpoints

Mild COVID-19	**Moderate COVID-19**	**Severe COVID-19**
New onset cough **OR** fever **OR** Two or more of following: • Shortness of breath • Fatigue, • Aches • Headache • Loss of taste/smell • New onset nausea/vomiting/diarrhea	Any of the following: • high fever (38.4 °C for 3 or more days) • Shortness of breath with exertion • Respiratory rate 24-29 breaths/minute • SPO_2 94-95% • Abnormal chest x-ray, • "Adventitious" sounds on lung exam	Any of the following: • Respiratory rate > 30 breaths/minute • Heart rate >125 beats/minute • SpO_2 less than 93% on room air • CPAP/BIPAP/high level ventilation • Renal/hepatic/right or left heart failure/stroke/thrombotic event • ICU admission • Death

Vaccines Authorized for Use Outside the US

Oxford-AstraZeneca vaccine
Type: Chimpanzee adenoviral vector
Doses: 2 doses, 28 days apart
Handling requirements: Store at 2°C to 8 °C
Regulatory status:
US: Undergoing licensure trial in US (separate from trials that lead to licensure in UK)

The Oxford-AstraZeneca chimpanzee adenoviral vector vaccine (ChAdOx1 NCoV-19 Vaccine, AZD1222) has a more complex regulatory path and is currently undergoing a trial intended to facilitate licensure in the US. The results of that trial are not yet available. The trials supporting licensure in the UK are listed below. Additional complexity is added by different dosing intervals and doses used during each clinical trial conducted to date.

UK and Brazil Cohorts:

- An interim analysis of two of the four ongoing phase 2/3 trials for the Oxford–AstraZeneca chimpanzee adenovirus vectored vaccine ChAdOx1 nCoV-19 (n=7,548 in UK trial, n=4,088 in Brazil trial) showed a vaccine efficacy of 62.1% (95%CI 41.0-75.7%) among participants who received the planned two standard doses (Voysey).
- A smaller number of participants (n=1367 in the vaccine group and 1374 in the placebo group) erroneously received a low initial dose followed by a standard second dose. The observed vaccine efficacy for the low-dose/standard dose combination was 90.0% (95% CI 67.4-97.0) (3 of 1,367 in the vaccine group vs 30 of 1,374 in the placebo group) (Voysey).
- The overall vaccine efficacy against symptomatic COVID-19 was 70.4% (95.8% CI 54.8-80.6%) (Voysey).
- The majority of participants included in this interim analysis were aged 18-55 (88%), white (83%), and female (61%).
- The efficacy the ChAdOx1 nCoV-19 vaccine against the B.1.1.7 variant of SARS-CoV-2 was similar to the efficacy against parent lineages, with 74% efficacy against B.1.1.7 compared to 84% efficacy against non- B.1.1.7 lineages (Emary). Vaccine-induced antibodies had an approximately nine-fold reduction in neutralization activity against the B.1.1.7 variant compared to a canonical non-B.1.1.7 lineage in a live-virus neutralization assay.
- Among those vaccinated with ChAdOx1 who subsequently became infected with SARS-CoV-2, both the duration of shedding and viral load was lower than among control participants (Emary).
- Exploratory analysis of interim data from trials of the Oxford-AstraZeneca vaccine suggested that lengthening the interval between vaccination doses was associated with increases in clinical efficacy (Voysey).
- In a subset of participants who elected not to receive the second dose, the efficacy of a single-dose was 76% and protection did not decline during the 3-month period following the initial vaccination (Voysey).
- Participants in the study also received weekly swabs to look for detectable nucleic acid in the absence of symptoms. Overall reduction in PCR+ samples was 54% (45%-62%), suggesting a potential for reduced transmissibility (Voysey).

Note: the South African study was stopped due to the apparent lack of activity against the mild disease caused by the B.1.3.5 variant. Data from this decision – including efficacy against severe disease – have not been made public to date.

Primary Endpoints by arm

Group	***Total enrolled***	***Clinical COVID-19***	***Hospitalized with COVID-19***
Placebo (pooled)	*8,581*	*248*	*15*
Vaccine (pooled)	*8,597*	*84*	*0*

Summaries of relevant articles:

Emary et al. (Feb 4, 2021). Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC. Pre-print downloaded Feb 5 https://ssrn.com/abstract=3779160

- *[Pre-print, not peer reviewed]* The efficacy the ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca; AZD1222) against the B.1.1.7 variant of SARS-CoV-2 was similar to the efficacy against parent lineages, with 74% efficacy (95% CI, 42-89%) against B.1.1.7 compared to 84% efficacy (95% CI, 71-91%) against non- B.1.1.7 lineages. Vaccine-induced antibodies had an approximately nine-fold reduction in neutralization activity against the B.1.1.7 variant compared to a canonical non-B.1.1.7 lineage in a live-virus neutralization assay.
- All participants received weekly nasal swabs for surveillance. Among those vaccinated with ChAdOx1 who subsequently became infected with SARS-CoV-2, both the duration of shedding and viral load was lower than among control participants. The authors suggest that this may result in a lower potential for transmission with vaccination.

Voysey et al. (Feb 19, 2021). Single-Dose Administration and the Influence of the Timing of the Booster Dose on Immunogenicity and Efficacy of ChAdOx1 NCoV-19 (AZD1222) Vaccine: A Pooled Analysis of Four Randomised Trials. The Lancet. https://doi.org/10.1016/S0140-6736(21)00432-3

- Pooled analysis of four randomized placebo-controlled trials (total n=24,422) of the Oxford-AstraZeneca ChAdOx1 nCov-19 (AZD1222) vaccine show that overall efficacy against symptomatic SARS-CoV-2 infection >14 days after the second dose was 66.7% (95%CI: 57.4-74.0%), with 84 cases (1% cumulative incidence) in the 8,597 participants in the vaccine group and 248 cases (2.9% cumulative incidence) in the 8,581 participants in the control group.
- Efficacy appears to have been greater when doses were administered ≥12 weeks apart. Among those receiving two standard doses, the vaccine efficacy after the second dose was 81.3% (95%CI: 60.3-91.2%) when doses were ≥12 weeks apart and 55.1% (95%CI: 33.0-69.9%) when doses were <6 weeks apart. Exploratory analyses showed that vaccine efficacy after a single standard dose of vaccine from day 22 to day 90 after vaccination was 76.0% (59.3–85.9%)
- Participants included in this pooled analysis were from studies in the UK (COV001) and (COV002), Brazil (COV003), and South Africa (COV005). *[EDITORIAL NOTE: A pre-print version of this analysis was summarized in this report on February 3, 2021.]*

Voysey et al. (Feb 1, 2021). Single Dose Administration , and the Influence of the Timing of the Booster Dose on Immunogenicity and Efficacy of ChAdOx1 NCoV-19 (AZD1222) Vaccine. SSRN. https://ssrn.com/abstract=3777268

- *[Pre-print, not peer-reviewed]* Exploratory analysis of interim data from the University of Oxford studies of the ChAdOx1 (Oxford-AstraZeneca) vaccine suggested that lengthening the interval between vaccination doses was associated with increases in clinical efficacy. In the standard dose group (since approved by the MHRA and other international regulators), the efficacy after the second dose was 82% at 12+ weeks, compared with 55% at <6 weeks and antibody responses were more than twice as high after 12+ weeks compared to <6 weeks among those who were 18-55 years of age. Due to a mishap with calculating the concentration of study product, a subset of participants had received a lower dose (LD) of the vaccine for the first dose (approximately one half of the intended dose) which did not affect clinical efficacy. Additionally, in a subset of participants who elected not to receive the second dose, the efficacy of a sole dose of the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) was 76% and protection did not decline during the 3-month period following the initial vaccination.
- Participants in the study also received weekly swabs to look for detectable nucleic acid in the absence of symptoms. Overall reduction in PCR+ samples was 54% (45%-62%), suggesting a potential for reduced transmissibility.

Voysey et al. (Dec 8, 2020). Safety and Efficacy of the ChAdOx1 NCoV-19 Vaccine (AZD1222) against SARS-CoV-2: An Interim Analysis of Four Randomised Controlled Trials in Brazil, South Africa, and the UK. The Lancet. https://doi.org/10.1016/S0140-6736(20)32661-1

- An interim analysis of two of the four ongoing phase 2/3 trials for the Oxford–AstraZeneca chimpanzee adenovirus vectored vaccine ChAdOx1 nCoV-19 (n=7,548 in UK trial, n=4,088 in Brazil trial) showed a vaccine efficacy of 62.1% (95%CI 41.0-75.7%) among participants who received the planned two standard doses (27 COVID-19 cases among 4,440 in the vaccine group and 71 COVID-19 cases among 4,455 in the placebo group).
- A smaller number of participants (n=1367 in the vaccine group and 1374 in the placebo group) erroneously received a low initial dose followed by a standard second dose. The observed vaccine efficacy for the low-dose/standard dose combination was 90.0% (95% CI 67.4-97.0) (3 of 1,367 in the vaccine group vs 30 of 1,374 in the placebo group). All of the participants who received the low-dose/standard dose combination were age 18-55, while 16% of those that received two standard doses were >55 years old.
- The overall vaccine efficacy against symptomatic COVID-19 was 70.4% (95.8% CI 54.8-80.6%), with no COVID-19-related hospital admissions occurring in vaccine recipients and 10 occurring in the control group at least 14 days after the second dose.
- The majority of participants included in this interim analysis were aged 18-55 (88%), white (83%), and female (61%)

Gamaleya (Sputnik V)

Type: Adenovirus viral vector

Doses: 2 doses, 21 days apart. Note: there are actually two adenoviruses used (first dose is recombinant adenovirus 26 followed by recombinant adenovirus 5).

Handling requirements: Stored at 2 °C to 8 °C

Logunov et al. (Feb 2, 2021). Articles 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. The Lancet. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00234-8/fulltext

- Interim analysis of the randomized, double-blind, placebo-controlled phase 3 trial for the recombinant adenovirus (rAd)-based vaccine Gam-COVID-Vac (Sputnik V) (n=19,866) showed an efficacy of 91.6% (CI: 85.6%-95.2%) by 21 days after the first dose of vaccine (the day of dose 2). 16 of 14,964 (0.1%) people in the vaccine group developed COVID-19 compared to 62 of 4,902 (1.3%) people in the placebo group**. Participants were required to be IgG/IgM negative at baseline for enrollment**. Rates of disease onset were similar for the vaccine and placebo groups until about 16 to 18 days after the first dose.
- The observed vaccine efficacy was >87% in all age and sex subgroups (60% male), and 91.8% in participants aged >60 years (11% of participants). 98.5% of participants were white, and the entire study was conducted in 25 hospitals and polyclinics in Moscow, Russia. 94% of reported adverse events were grade 1, with 0.3% and 0.4% of vaccine and placebo group experiencing serious adverse events, respectively.

Definition of primary endpoints

Mild COVID-19	Moderate COVID-19	Severe COVID-19	Extremely Severe COVID-19
• Cough, weakness, sore throat • "No symptoms of moderate and severe course"	• Fever over 38.5C • Respiratory rate >28 breaths per minute • Shortness of breath during physical exertion • Pneumonia (confirmed by computed tomography of lungs) • Oxygen saturation less than 95% • C-reactive protein of blood serum more than 10mg/L	• Respiratory Rate more than 22 breaths/minute • Oxygen saturation level <93% • Progression of changes in the lungs according to Xray, CT, or ultrasonography • Decreased level of consciousness, agitation • Unstable hemodynamics • Arterial blood lactate >2mmol/liter • More than 2 points on the Sequential Organ Failure Score	• Acute respiratory failure with need for invasive mechanical ventilation • Septic Shock • Multiple organ failure • Changes in the lungs on CT typical of critical viral lesion or evidence of acute respiratory distress syndrome (ARDS)

Sinovac: CoronaVac
Type: inactivated
Doses: 2 doses, 14 days apart
Handling requirements: Stored at 2 °C to 8 °C

Note neither the underlying protocol nor the underlying data were made publicly available at present.

Press release: "As of December 16, 2020, there were 12,396 health workers over 18 years old enrolled. A total of 253 positive cases were collected during the observation period. After 14 days following vaccination with 2 doses of vaccine following a 0, 14 day schedule, the efficacy rate against diseases caused by COVID-19 was 50.65% for all cases, 83.70% for cases requiring medical treatment, and 100.00% for hospitalized, severe, and fatal cases."

Wu et al. (Feb 3, 2021). Safety, Tolerability, and Immunogenicity of an Inactivated SARS-CoV-2 Vaccine (CoronaVac) in Healthy Adults Aged 60 Years and Older: A Randomised, Double-Blind, Placebo-Controlled, Phase 1/2 Clinical Trial. The Lancet Infectious Diseases.
https://www.thelancet.com/article/S1473-3099(20)30843-4/fulltext

- In a randomized, double-blind, placebo-controlled phase 1/2 trial of the inactivated SARS-CoV-2 vaccine CoronaVac conducted among healthy, seronegative adults aged ≥60 years (n=421), all adverse reactions were mild or moderate, with injection site pain as the most frequently reported reaction (9%). Seroconversion after two doses was reported in at least 90% of all dosage groups and none in the placebo groups.

Additional Trials in Populations of Interest

Persons with prior COVID Infection

Emerging evidence strongly suggests that persons with a prior history of SARS-CoV-2 infection develop a robust anamnestic response upon vaccination (Bradley, Krammer, Abu Jabal).

Summaries of relevant articles:

Bradley et al. (Feb 5, 2021). Antibody Responses Boosted in Seropositive Healthcare Workers after Single Dose of SARS-CoV-2 MRNA Vaccine. Pre-print downloaded Feb 8 from https://doi.org/10.1101/2021.02.03.21251078

- Among healthcare workers who received a single dose of the Pfizer/BioNTech vaccine, those who had SARS-CoV-2 infection 30-60 days prior to vaccination (n = 36) had significantly higher antibody levels at 3 weeks post-vaccination than individuals with no prior infection (n = 152).
- After the first vaccine dose, both previously infected and uninfected individuals' antibody titers were enhanced to all proteins (S1, S2, RBD) with the exception of the nucleocapsid protein, which is not a vaccine antigen.

Krammer et al. (Jan 1, 2021). Robust Spike Antibody Responses and Increased Reactogenicity in Seropositive Individuals after a Single Dose of SARS-CoV-2 MRNA Vaccine. Pre-print downloaded Feb 1 from https://www.medrxiv.org/content/10.1101/2021.01.29.21250653v1

- [Pre-print, not peer-reviewed] One dose of mRNA vaccine elicited a rapid and strong immune response among individuals already seropositive for SARS-CoV-2, with antibody titers 10-20 times higher than those of naïve vaccinees at the same timepoint.
- Seropositive individuals also had antibody titers that exceeded by >10-fold the median titers among individuals without previous infection who received two doses of the vaccine.
- Among 109 individuals who received their first vaccine dose in 2020, variable and low IgG responses were observed 9-12 days after vaccination among those who were seronegative(n=68), while uniformly high antibody titers were observed within 5-8 days among those who were seropositive (n=41).

Abu Jabal et al. (Feb 11, 2021). Impact of Age, Ethnicity, Sex and Prior Infection Status on Immunogenicity Following a Single Dose of the BNT162b2 MRNA COVID-19 Vaccine: Real-World Evidence from Healthcare Workers, Israel, December 2020 to January 2021. Eurosurveillance. https://doi.org/10.2807/1560-7917.ES.2021.26.6.2100096

- A single dose of the Pfizer SARS-CoV-2 vaccine produced detectable anti-SARS-CoV-2 spike IgG antibodies 21 days after vaccination in 92% (n=475) of a cohort of healthcare workers in Israel, including in 92% (n=458) of people who had no history of COVID-19 infection. The 39 healthcare workers who did not respond to the first dose were older (mean age 57) than those who did (mean age 45). Among those with antibodies after vaccination, IgG titers decreased with increasing age, although the authors note that the decrease was small and of unclear clinical significance. In people with a history of COVID-19, the single vaccine dose was associated with

IgG titres approximately one order of magnitude higher compared with vaccinated individuals with no prior history of COVID-19.