

Synthesis Summary

COVID-19 Vaccines

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COVID-19 Literature Report Team:

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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](#).

Text marked in **BLUE** is new since the last version of this summary.

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.**
- **Emerging evidence suggests that currently authorized vaccines have high effectiveness in real-world settings.**
- **All currently authorized vaccines have shown effectiveness against the B.1.1.7 SARS-CoV-2 variant.**

- **Efficacy against the B.1.351 variant was very low (~10%) for the Oxford-AztraZeneca, but comparable to other variants for the Johnson & Johnson and Novavax vaccines.**
- **The currently authorized vaccines prevent asymptomatic infection and reduce the risk of transmission among those who become infected following vaccination.**

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 [April 2, 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.CO2.S from **Johnson & Johnson-Janssen** (1 dose)

Another candidate vaccine currently undergoing phase III trials to support licensure in the United States is from **Novovax** (a two-dose regimen) ([Shinde](#)). 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**), **Gamaleya** Research Institute in Russia (**Sputnik V**), and **Bharat Biotech**. 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.

Trials of vaccines authorized for use in the US for those 16 years of age and older are now undergoing trials in younger people. Preliminary results from a trial of the Pfizer-BioNTech vaccine showed 100% efficacy against COVID-19 among adolescents (n=2,260) aged 12 to 15 years old in the US without prior history of infection.

Real-World Vaccine Effectiveness

The high trial efficacy (85% to 95%) of vaccines currently approved for use in the US, as well as the Oxford-AstraZeneca vaccine authorized in Europe, the UK, and elsewhere, has been mirrored by similarly high real-world effectiveness, including against the B.1.1.7 variant ([Thompson](#), [Benenson](#), [Lumley](#), [Rinott](#), [Dagan](#)). Vaccination as appears to be effective at preventing asymptomatic infection ([Tande](#)). At least over a relatively short period of follow-up, partial vaccination with only one dose of the Pfizer-BioNTech, Moderna, and Oxford-AstraZeneca has shown a level of effectiveness that is slightly lower but approaching the level of protection seen with full vaccination ([Bouton](#), [Yelin](#), [Britton](#), [Krammer](#), [Moustsen-Helms](#), [Bernal](#), [Saul](#), [Manisty](#), [Romero-Brufau](#)). The authorized vaccines have performed well across various patient populations, including residents of nursing homes ([Hollinghurst](#), [Moustsen-Helms](#), [Britton](#)) and pregnant and breastfeeding women ([Gray](#)), although there has been some evidence of lower immune responses among nursing home residents ([Canaday](#)), among older individuals ([Müller](#)), those who have received solid organ transplants, and others with chronic medical conditions ([Simon](#), [Yelin](#), [Pellini](#)). Vaccine-induced antibodies been detected in cord blood and in breastmilk ([Gray](#), [Baird](#)). Vaccination also results in a lower viral load among those who have been vaccinated and have subsequently become infected, including those who have been infected following first dose, and before they have received their second dose ([McEllistrem](#)). Vaccine responses following a first vaccine dose have been stronger among those who have been previously infected with SARS-CoV-2 compared those with not prior infection history ([Eyre](#), [Bradley](#), [Demonbreun](#), [Predecki](#)). This high level of vaccine effectiveness, including against asymptomatic infection, lead the CDC to release recommendations that fully vaccinated individuals can now safely gather indoors with other fully vaccinated individuals without wearing a mask ([CDC](#)).

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](#), [Blumenthal](#))
- 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](#), [Blumenthal](#)). 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](#)).

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 as 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. However, there is emerging evidence that increases in the proportion of the population that is immunized is associated with decreases in the incidence of SARS-CoV-2 in unvaccinated people ([Milman](#)), and vaccination is associated in a lower viral load among those who subsequently become infected, including those infected 12-37 days after the first vaccine dose ([Levine-Tiefenbrun](#), [Saad-Roy](#)). 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](#)).

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 [evidence of the](#) 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. [The Novavax vaccine, which is pending authorization, showed 50% efficacy overall and 60% efficacy in people who were HIV-negative in trials in South Africa, where the B.1.351 variant accounting for vast majority of infections in participants in both the placebo and vaccine arms \(\[Shinde\]\(#\)\). Across all of the currently authorized vaccines, efficacy appears to be similar against the B.1.1.7 variant \(first described in the UK\) compared to other viral lineages \(\[Emary\]\(#\)\).](#)

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](#), [Supasa](#), [Edara](#), [Chang](#), [Trinite](#)). 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](#), [Fisher](#), [Becker](#), [Chen](#)) and authors have expressed concerns that this could indicate lower vaccine efficacy against B.1.351. Evidence has varied regarding the susceptibility of the P.1 variant, which was first described in Brazil, to vaccine-induced neutralization, but it appears that P.1 may be more susceptible to vaccine neutralization than the B.1.351 variant ([Dejinrattisai](#), [Wang](#)). However, the relationship between levels of in vitro neutralization and actual vaccine efficacy remains unclear and there is no currently accepted correlate of immunity.

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
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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 <u>OR</u> >48 hours of any of the following: <ul style="list-style-type: none"> • Shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours) • Cough (of any duration, including ≤ 48 hours) • Fatigue • Muscle or body aches • Headache • New loss of taste or smell • Sore throat • Congestion or runny nose • Nausea or vomiting • Diarrhea 	Not defined	Any of the following: <ul style="list-style-type: none"> • Respiratory rate >30 breaths/minute • Heart rate >125 beats per minutes • Blood oxygen (SpO₂) less than 93% • Respiratory failure or acute respiratory distress syndrome (ARDS) • Shock • Acute renal, hepatic, or neurologic dysfunction • ICU admission or death

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: <ul style="list-style-type: none"> Fever, Cough Shortness of breath Chills Muscle pain Sore throat Diarrhea Vomiting 	Not defined	Any of the following: <ul style="list-style-type: none"> Respiratory rate >30 breaths/minute Heart rate >125 beats/minute shock acute renal, hepatic or neurologic dysfunction ICU admission Death

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

Group	Total Enrolled	Moderate to severe/critical COVID-19		Severe/critical COVID-19	
		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

Group	Total Enrolled	Moderate to severe/critical COVID-19		Severe/critical COVID-19	
		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: <ul style="list-style-type: none"> • Fever ($\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$), • 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. 	<ul style="list-style-type: none"> • 3 or more symptoms (see mild COVID-19) <p>OR</p> Any one of the following new or worsening signs/symptoms: <ul style="list-style-type: none"> • Respiratory rate ≥ 20 breaths/minute • Abnormal SpO₂ but still $>93\%$ 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 <ul style="list-style-type: none"> • Fever ($\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) • Heart rate ≥ 90 beats/minute • Shaking chills or rigors • Sore throat • Cough • Malaise • Headache • Muscle pain (myalgia) • Gastrointestinal symptoms 	Clinical signs at rest indicative of severe systemic illness: <ul style="list-style-type: none"> • Respiratory rate ≥ 30 breaths/minute • Heart rate ≥ 125 beats/minute • SpO₂ $\leq 93\%$ 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

	<ul style="list-style-type: none"> • New or changing olfactory or taste disorder • Red or bruised looking feet or toes 	
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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)	<i>Approx. half of "15000"</i>	56	61	1
Vaccine (UK)	<i>Approx. half of "15000"</i>	6	6	0
Placebo (South Africa)	<i>Approx. half of "Over 4400"</i>	29	29	0
Vaccine (South Africa)	<i>Approx. half of "Over 4400"</i>	15	14	1

Definition of primary endpoints

Mild COVID-19	Moderate COVID-19	Severe COVID-19
<p>New onset cough OR fever OR Two or more of following:</p> <ul style="list-style-type: none"> • Shortness of breath • Fatigue, • Aches • Headache • Loss of taste/smell • New onset nausea/vomiting/diarrhea 	<p>Any of the following:</p> <ul style="list-style-type: none"> • high fever (38.4 °C for 3 or more days) • Shortness of breath with exertion • Respiratory rate 24-29 breaths/minute • SPO₂ 94-95% • Abnormal chest x-ray, • “Adventitious” sounds on lung exam 	<p>Any of the following:</p> <ul style="list-style-type: none"> • Respiratory rate > 30 breaths/minute • Heart rate >125 beats/minute • SpO₂ 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

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](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
<ul style="list-style-type: none"> • Cough, weakness, sore throat • “No symptoms of moderate and severe course” 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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

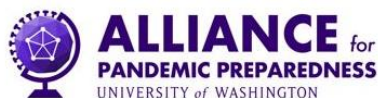
Type: inactivated

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



Updated 4/2/2021

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](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.

Other Candidate Vaccines

Bharat Biotech whole-virion inactivated SARS-CoV-2 vaccine

Type: inactivated

Doses: 2 doses, 14 days apart

Ella et al. (Mar 8, 2021). Safety and Immunogenicity of an Inactivated SARS-CoV-2 Vaccine, BBV152: Interim Results from a Double-Blind, Randomised, Multicentre, Phase 2 Trial, and 3-Month Follow-up of a Double-Blind, Randomised Phase 1 Trial. The Lancet Infectious Diseases. [https://doi.org/10.1016/S1473-3099\(21\)00070-0](https://doi.org/10.1016/S1473-3099(21)00070-0)

- Interim results from a double-blind randomized phase 2 trial (n=380) of the Bharat Biotech whole-virion inactivated SARS-CoV-2 vaccine (BBV152) show robust neutralizing titers against wild-type SARS-CoV-2 at day 56 following two doses administered on day 0 and day 28. In a plaque-reduction neutralization test, the 6 µg dose group compared to the 3 µg dose group had higher geometric mean neutralizing titers (197 vs 100) and higher proportion of seroconversion (98% vs 93%) at day 56. No significant difference was observed in the proportion of participants who reported local or systematic adverse reactions between the dose groups (20% vs 21%), and no serious adverse events were reported in the study.

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](#)).

Vaccine Uptake and Acceptance

Stern et al. (Apr 2, 2021). Willingness to Receive a COVID-19 Vaccination Among Incarcerated or Detained Persons in Correctional and Detention Facilities — Four States, September–December 2020. MMWR. <https://doi.org/10.15585/mmwr.mm7013a3>

- The COVID-19 vaccination refusal rate was 45% among 5,110 surveyed residents of three prisons and 13 jails across four states during September to December 2020 (all three prisons and 10 jails in Washington State). The most common reason for vaccination refusal was distrust of health care, correctional, or government personnel or institutions (20%). 10% of surveyed residents expressed vaccine hesitancy; waiting for more information was the most common reason for hesitancy (55%). Willingness to be vaccinated was lowest among Black participants (37%; 510 of 1,390), participants aged 18–29 years (39%; 583 of 1,516), and those who lived in jails versus prisons (44%; 1,850 of 4,232).

Grumbach et al. (Mar 30, 2021). Association of Race/Ethnicity With Likelihood of COVID-19 Vaccine Uptake Among Health Workers and the General Population in the San Francisco Bay Area. JAMA Internal Medicine. <https://doi.org/10.1001/jamainternmed.2021.1445>

- Black, Latinx, and Asian employees of three large medical centers in San Francisco had lower odds of reporting that they were likely to get vaccinated against COVID-19 compared to white employees in a cross-sectional study conducted from November 2020 to January 2021 (n=1,803). Compared to white respondents, Black, Asian and Latinx had 50%, 63%, and 72% lower odds for likelihood of vaccine uptake, respectively. Similarly, ethnic minorities in a general population cohort (n=3,161) residing in counties in the San Francisco Bay Area reported lower odds for likelihood of vaccine uptake compared to white respondents. While ratings of reasons to get vaccinated were similar across racial/ethnic groups, minorities were significantly more likely than white respondents to endorse reasons not to get vaccinated, such as less confidence in vaccine efficacy, less trust in vaccine manufacturers, and more worry that government process were rushed.

Lindemer et al. (Mar 26, 2021). Counties with Lower Insurance Coverage Are Associated with Both Slower Vaccine Rollout and Higher COVID-19 Incidence across the United States. Pre-print downloaded Mar 29 from <https://doi.org/10.1101/2021.03.24.21254270>

- [Pre-print, not peer-reviewed] US counties with high levels of uninsured individuals had significantly lower COVID-19 vaccination rates and tended to have the highest COVID-19 incidence rates in March 2021 relative to December 2020, according to an analysis of data from over 1,500 counties (228 million individuals). Counties with higher percentages of Black and Hispanic individuals also had significantly lower vaccination rates, and smaller declines in COVID-incidence rates.

Kriss et al. (Mar 15, 2021). COVID-19 Vaccine Second-Dose Completion and Interval Between First and Second Doses Among Vaccinated Persons — United States, December 14, 2020–February 14, 2021. MMWR. <https://doi.org/10.15585/mmwr.mm7011e2>

- Vaccination data reported to CDC indicate that among people who received the first dose of either the Moderna or Pfizer/BioNTech vaccines as of February 14, 2021, and for whom enough time had elapsed to receive the second dose, 88.0% had completed the series and 8.6% had not received the second dose. Among all people who received 2 doses, 95.6% received the second dose within the

recommended time interval (Pfizer-BioNTech 1-25 days and Moderna 24-32 days since the first dose). The percentage of people who missed the second dose varied by geographic area (range = 0.0%–9.1%).

Jain et al. (Mar 12, 2021). A Rapid Review of COVID-19 Vaccine Prioritization in the U.S. Alignment between Federal Guidance and State Practice. Pre-print downloaded Mar 15 from <https://doi.org/10.1101/2021.03.11.21253411>

- *[Pre-print, not peer-reviewed]* A study assessing variability in vaccine priority groups between state and federal guidance found that while state plans largely prioritized healthcare workers and residents of long-term care facilities (consistent with federal guidelines), essential workers were often excluded from state priority plans. Of 37 states that included frontline essential workers, 12 assigned them to a lower priority than recommended by federal guidance. Almost all states prioritized individuals ages 65-74 years, and most assigned them to a higher position than recommended in federal guidance. Some groups not considered high priority in federal guidelines, such as people living in congregate settings or with disabilities, were highly prioritized by 38 states.

Chapman et al. (Mar 8, 2021). Comparison of COVID-19 Vaccine Prioritization Strategies in the United States. Pre-print downloaded Mar 10 from <https://doi.org/10.1101/2021.03.04.21251264>

- *[Pre-print, not peer-reviewed]* A static simulation model using California as an example to compare the impact of different vaccine prioritization strategies in the United States found that prioritizing older individuals averted the highest proportion of disability-adjusted life years (DALYs, 40% for 5 million individuals vaccinated) and deaths (65%), but the lowest proportion of cases (12%). Prioritizing essential workers averted the lowest proportion of DALYs (25%) and deaths (33%). Allocating vaccines simultaneously by age and location or multiple factors (age, sex, race/ethnicity, location, occupation, and comorbidity status) averted a significantly higher proportion of DALYs (48% and 56%) than any strategy prioritizing by a single risk factor. The authors note that their approach may underestimate the impact of vaccination by not incorporating onward transmission.

Summaries of relevant articles

Reverse chronological order within topical categories

Overview of Vaccine Efficacy Trials

- *[Press release, not peer-reviewed]* According to a press release from Pfizer, the Pfizer-BioNTech vaccine showed 100% efficacy against COVID-19 among adolescents (n=2,260) aged 12 to 15 years old in the US without prior history of infection. 18 cases of COVID-19 were observed in the placebo group, and none in the vaccinated group. The vaccine also elicited a strong neutralizing antibody response (geometric mean titers 1,239.5) one month after the second dose, and side effects were similar to those observed among participants aged 16-25 in previous trials. The press release notes that the companies plan to submit these data to the FDA and request an amendment to the Emergency Use Authorization to expand eligibility to adolescents aged 12-15.
Pfizer Inc. (2021). Pfizer-BioNTech Announce Positive Topline Results of Pivotal COVID-19 Vaccine Study in Adolescents. <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-biontech-announce-positive-topline-results-pivotal>
- Post-hoc analysis of the Oxford-AstraZeneca vaccine indicated that clinical vaccine efficacy against symptomatic, PCR-positive infection was 70.4% for the B.1.1.7 variant and 81.5% for non-B.1.1.7 lineages (not including the B.1.351 variant). Neutralization activity via vaccine-induced antibodies *in vitro* was also lower against the B.1.1.7 variant (geometric mean ratio 8.9). Participants 18 and older in efficacy cohorts (n=8534) were included in the analysis, and received either the COVID-19 vaccine or a control meningococcal conjugate vaccine. *[EDITORIAL NOTE: This paper was summarized as a pre-print on February 5, 2021]*
Emary et al. (Mar 30, 2021). Efficacy of ChAdOx1 NCoV-19 (AZD1222) Vaccine against SARS-CoV-2 Variant of Concern 202012/01 (B.1.1.7): An Exploratory Analysis of a Randomised Controlled Trial. The Lancet. [https://doi.org/10.1016/S0140-6736\(21\)00628-0](https://doi.org/10.1016/S0140-6736(21)00628-0)

Real-World Vaccine Effectiveness

Bouton et al. (Mar 31, 2021). COVID-19 Vaccine Impact on Rates of SARS-CoV-2 Cases and Post Vaccination Strain Sequences among Healthcare Workers at an Urban Academic Medical Center a Prospective Cohort Study. Pre-print downloaded Apr 1 from <https://doi.org/10.1101/2021.03.30.21254655>

- *[Pre-print, not peer-reviewed]* Among a cohort of healthcare workers (HCW) from Boston Medical Center who received the first dose of either the Pfizer-BioNTech or Moderna vaccines, the SARS-CoV-2 infection rate was 27% and 82% lower 1-14 days and >14 days after receiving the first dose, respectively, compared to surrounding community infection rates. SARS-CoV-2 infections occurred in 1.4% (96 of 7109) of HCWs given at least a first dose and 0.3% (17 of 5913) of HCWs given both doses. SARS-CoV-2 infections >14 days from the first dose were more frequently asymptomatic,

among older HCWs, and HCWs of Latinx ethnicity. Analysis of 48 SARS-CoV-2 genomes sequenced from first-dose infections did not indicate selection pressure towards mutations in the spike protein known to escape antibody neutralization.

Eyre et al. (Mar 26, 2021). Quantitative SARS-CoV-2 Anti-Spike Responses to Pfizer-BioNTech and Oxford-AstraZeneca Vaccines by Previous Infection Status. Pre-print downloaded Mar 29 from <https://doi.org/10.1101/2021.03.21.21254061>

- [Pre-print, not peer-reviewed] Vaccination with either the Pfizer-BioNTech or Oxford-AstraZeneca vaccines led to detectable anti-spike antibodies in nearly all participants in a study of adult healthcare workers (HCWs) in the UK. 3570/3610 (98.9%) HCWs were seropositive >14 days post-first vaccination and prior to second vaccination, 2706/2720 (99.5%) after Pfizer-BioNTech and 864/890 (97.1%) following Oxford-AstraZeneca vaccines. HCWs who had previously been infected or were younger were more likely to test seropositive post-first vaccination, with no evidence of differences by sex or ethnicity, and all HCWs tested >14 days after the second vaccine were seropositive. Antibody responses post-second vaccination were similar to those after prior infection and one vaccine dose.

Simon et al. (Mar 26, 2021). Hemodialysis Patients Show a Highly Diminished Antibody Response after COVID-19 mRNA Vaccination Compared to Healthy Controls. Pre-print downloaded Mar 29 from <https://doi.org/10.1101/2021.03.26.21254259>

- [Pre-print, not peer-reviewed] Patients receiving hemodialysis had significantly lower anti-SARS-CoV-2 antibody titers than healthy controls 21 days after vaccination with the Pfizer-BioNTech vaccine (171 U/ml versus 2500 U/ml, respectively), according to a prospective cohort study (n = 81 patients, 80 controls). There was no correlation between antibody responses to the Hepatitis B vaccine and the SARS-CoV-2 vaccine.

Thompson et al. (Mar 29, 2021). Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March. MMWR. <https://doi.org/10.15585/mmwr.mm7013e3>

- The mRNA vaccines (Pfizer-BioNTech and Moderna) were 90% effective at preventing SARS-CoV-2 infection after full immunization (≥ 14 days after second dose) and 80% after partial immunization (≥ 14 days after first dose but before second dose), according to interim estimates among 3,950 healthcare personnel, first responders, and other essential and frontline workers in multiple locations across the US. Study participants completed weekly SARS-CoV-2 testing for 13 consecutive weeks, from December 14-18, 2020 to March 13, 2021.

McEllistrem et al. (Mar 26, 2021). Single Dose of a mRNA SARS-CoV-2 Vaccine Is Associated with Lower Nasopharyngeal Viral Load among Nursing Home Residents with Asymptomatic COVID-19. Clinical Infectious Diseases. <https://doi.org/10.1093/cid/ciab263>

- Among nursing home residents in Pennsylvania with asymptomatic COVID-19 diagnosed through twice-weekly surveillance testing, residents who received a single dose of the BNT162b2 (Pfizer-BioNTech) vaccine had significantly lower nasopharyngeal viral load (-2.4 mean \log_{10} lower) than

unvaccinated residents. The authors note their results suggest a single dose may start to reduce transmission among nursing home residents.

Benenson et al. (Mar 23, 2021). BNT162b2 MRNA Covid-19 Vaccine Effectiveness among Health Care Workers. New England Journal of Medicine. <https://doi.org/10.1056/NEJMc2101951>

- Weekly incidence of COVID-19 among healthcare workers (HCWs) in a two-campus medical center in Jerusalem steadily declined after commencement of two-dose vaccinations with the Pfizer-BioNTech vaccine in December 2020. Decline in incidence occurred despite a surge of the B.1.1.7 variant (up to 80% of cases) within the community.

Bradley et al. (Mar 23, 2021). Antibody Responses after a Single Dose of SARS-CoV-2 mRNA Vaccine. New England Journal of Medicine. <https://doi.org/10.1056/NEJMc2102051>

- 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 and higher levels of antibodies with neutralizing characteristics 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. [EDITORIAL NOTE: A pre-print version of this manuscript was summarized in this report on February 8, 2021.]

Hollinghurst et al. (Mar 24, 2021). COVID-19 Infection Risk amongst 14104 Vaccinated Care Home Residents A National Observational Longitudinal Cohort Study in Wales United Kingdom December 2020 to March 2021. Pre-print downloaded Mar 25 from <https://doi.org/10.1101/2021.03.19.21253940>

- [Pre-print, not peer-reviewed] Only 1% of over 14,000 nursing home residents in the UK who have received the first dose of either the Pfizer-BioNTech or Oxford-AstraZeneca vaccines reported a positive SARS-CoV-2 PCR test in an observational study from December 2020 to March 2021. 90% of infections occurred within 28 days of the first dose. At 7 days post vaccination, those with prior infection had a 46% reduced hazard of a having a positive PCR. Those who received the Pfizer-BioNTech vaccine had a 3.8-fold higher hazard of having a positive test as compared to recipients of the Oxford-AstraZeneca vaccine. At 21 days post-vaccination, individuals with low or intermediate frailty (compared to high frailty) had 4.6- and 4.9-fold higher hazard of a positive PCR test, respectively.

Canaday et al. (Mar 22, 2021). Reduced BNT162b2 MRNA Vaccine Response in SARS-CoV-2-Naive Nursing Home Residents. Pre-print downloaded Mar 23 from <https://doi.org/10.1101/2021.03.19.21253920>

- [Pre-print, not peer-reviewed] Nursing home (NH) residents had blunted antibody responses following vaccination with BNT162b2 mRNA vaccine (Moderna) when compared to healthcare workers. SARS-CoV-2-naive NH residents mounted antibody responses with nearly 4-fold lower median neutralization titers and half the anti-spike level compared to SARS-CoV-2-naive healthcare workers. In contrast, NH residents who had recovered from infection and were subsequently vaccinated had neutralization, anti-spike, and anti-RBD titers similar to healthcare workers who had recovered from infection and were subsequently vaccinated.

Yelin et al. (Mar 17, 2021). Associations of the BNT162b2 COVID-19 Vaccine Effectiveness with Patient Age and Comorbidities. Pre-print downloaded Mar 17 from <https://doi.org/10.1101/2021.03.16.21253686>

- [Pre-print, not peer-reviewed] Effectiveness of the Pfizer-BioNTech vaccine gradually increased starting at 12 days after the first vaccine dose and then plateaued around 35 days, according to an analysis of electronic health records from 1.79 million individuals in Israel. This period of maximum effectiveness corresponds to a period 2-weeks after the scheduled administration of the second dose and resulted in 91.2% efficacy for prevention of all infections and 99.3% for prevention of symptomatic infections. Effectiveness declined with age and for patients with type 2 diabetes and effectiveness was the same for men and women.

Lumley et al. (Mar 12, 2021). An Observational Cohort Study on the Incidence of SARS-CoV-2 Infection and B.1.1.7 Variant Infection in Healthcare Workers by Antibody and Vaccination Status. Pre-print downloaded Mar 15 from <https://doi.org/10.1101/2021.03.09.21253218>

- [Pre-print, not peer-reviewed] A longitudinal cohort study of healthcare workers (HCWs) in England showed that both natural infection and vaccination (two doses of Pfizer/BioNTech or Oxford/AstraZeneca vaccine) provided more than 85% protection against symptomatic and asymptomatic SARS-CoV-2 infection, including with the B.1.1.7 variant. No HCWs who had received both doses had symptomatic infection, and incidence was 98% lower among seropositive HCWs (aIRR = 0.02). Two vaccine doses or seropositivity reduced the incidence of any PCR-positive result with or without symptoms by 90% and 85%, respectively. Single-dose vaccination was slightly less effective and reduced the incidence of symptomatic infection by 67% and any PCR-positive result by 64%.

Britton et al. (Mar 15, 2021). Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine Among Residents of Two Skilled Nursing Facilities Experiencing COVID-19 Outbreaks — Connecticut, December 2020–February 2021. MMWR. <https://doi.org/10.15585/mmwr.mm7011e3>

- Partial vaccination with the Pfizer-BioNTech COVID-19 vaccine (from >14 days after dose 1 through 7 days after dose 2) was found to be 63% effective against SARS-CoV-2 infection among residents of two skilled nursing facilities in Connecticut that experienced outbreaks from December 2020 – February 2021. Vaccine efficacy was similar (60%) when residents with prior SARS-CoV-2 infection were excluded. The retrospective cohort study determined that 97 cases of SARS-CoV-2 infection occurred during the outbreaks, including 40 (41%) at facility A and 57 (59%) at facility B. By the end of the study, most residents (304, 66%) received 2 vaccine doses, 72 (16%) received only 1 dose, and 87 (19%) were not vaccinated.

Tande et al. (Mar 10, 2021). Impact of the COVID-19 Vaccine on Asymptomatic Infection Among Patients Undergoing Pre-Procedural COVID-19 Molecular Screening. *Clinical Infectious Diseases*. <https://doi.org/10.1093/cid/ciab229>

- The risk of asymptomatic SARS-CoV-2 infection was significantly lower among patients who had received at least 1 dose of an mRNA COVID-19 vaccine compared to unvaccinated patients, based on a retrospective cohort study of asymptomatic adult patients (n=39,156) across multiple US states undergoing a pre-procedural SARS-CoV-2 molecular screening test. SARS-CoV-2 was detected in 3% of unvaccinated patients, compared to 1% of participants who had received at least dose prior to

screening. After adjusting for age, sex, race/ethnicity and location, the risk for a positive test was significantly lower for patients who had received their first dose >10 days earlier (aRR= 0.49) and those who had received their second dose >0 days (aRR=0.27) compared to unvaccinated patients.

Krammer et al. (Mar 10, 2021). Antibody Responses in Seropositive Persons after a Single Dose of SARS-CoV-2 MRNA Vaccine. New England Journal of Medicine. <https://doi.org/10.1056/NEJMc2101667>

- After a single dose of either the Pfizer-BioNTech or Moderna vaccine, US vaccinees with prior SARS-CoV-2 infection (n=43) had antibody titers 10-45 times as high as those of vaccinees without prior SARS-CoV-2 infection (n=67), according to interim results of a longitudinal study. While titers of those with prior infection did not increase after the second dose, median antibody titers were 6-fold higher than those without prior infection. No substantial difference was noted in the dynamics of antibody responses elicited by the Pfizer-BioNTech and Moderna vaccines after the first dose.
- In separate analyses within the larger longitudinal study, vaccine side effects after the first dose occurred more frequently among vaccinees with prior infection. [EDITORIAL NOTE: A pre-print related to this manuscript was summarized on February 1, 2020]

Moustsen-Helms et al. (Mar 9, 2021). Vaccine Effectiveness after 1st and 2nd Dose of the BNT162b2 MRNA Covid-19 Vaccine in Long-Term Care Facility Residents and Healthcare Workers - a Danish Cohort Study. Pre-print downloaded Mar 10 from <https://doi.org/10.1101/2021.03.08.21252200>

- [Pre-print, not peer-reviewed] A retrospective registry- and population-based observational cohort study in Denmark estimated that the Pfizer-BioNTech vaccine efficacy within 7 days of receipt was 52% among long term care facility residents (LTCF, n = 39,040) and 46% among health care workers (HCW, n = 331,039), which increased to 64% and 90%, respectively, beyond 7 days of immunization. No protective effect was observed for LTCF residents after the first dose. Among HCW, efficacy was 17% > 14 days after first dose (before second dose). During a median follow-up of 53 days, there were 488 and 5,663 confirmed SARS-CoV-2 cases in the unvaccinated groups, with 57 among LTCF residents and 52 among HCW within the first 7 days following the second dose, and 27 and 10 cases beyond seven days after the second dose.

U.S. Centers for Disease Control and Prevention. (Mar 8, 2021). When You've Been Fully Vaccinated. CDC. <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html>

- New recommendations from CDC indicate that fully vaccinated individuals can now safely gather indoors with other fully vaccinated individuals without wearing a mask, in light of the increasing evidence that vaccinated individuals are less likely to have asymptomatic infection and to transmit SARS-CoV-2 to others. In contrast, CDC recommends that fully vaccinated individuals only gather indoors and unmasked with *unvaccinated* people if they are from only one other household and no one is at increased risk for severe illness from COVID-19.
- The CDC still recommends taking COVID-19 precautions, such as wearing a mask in public, avoiding gatherings with unvaccinated people from multiple households and other medium to large-sized gatherings, and delaying travel.
- Following a confirmed COVID-19 exposure, the CDC recommends that fully vaccinated individuals must still isolate themselves if they experience symptoms, but do not need to quarantine or be tested if they remain asymptomatic.

- An individual is considered fully vaccinated 2 weeks after their second dose in a 2-dose series (e.g. Pfizer-BioNTech and Moderna vaccine) or 2 weeks after a single-dose vaccine (e.g. Johnson & Johnson vaccine).

Gray et al. (Mar 8, 2021). COVID-19 Vaccine Response in Pregnant and Lactating Women a Cohort Study. Pre-print downloaded Mar 9 from <https://doi.org/10.1101/2021.03.07.21253094>

- [Pre-print, not peer-reviewed] The Pfizer-BioNTech and Moderna vaccines elicited similar immune responses among pregnant (n=84) and lactating (n=31) women compared to non-pregnant reproductive-age women (n=16). All vaccine-induced SARS-CoV-2-specific antibody titers were higher compared to titers from a group of pregnant women (n=37) that had SARS-CoV-2 infection 4-12 weeks prior. Vaccine-induced antibodies were detected in all umbilical cord blood (n=10) and breastmilk samples (n=31), although only IgG and not IgA antibodies were increased in maternal blood and breastmilk following vaccination. No differences were noted in reactogenicity across the groups.

Demonbreun et al. (Mar 8, 2021). Comparison of IgG and Neutralizing Antibody Responses after One or Two Doses of COVID-19 mRNA Vaccine in Previously Infected and Uninfected Persons. Pre-print downloaded Mar 8 from <https://doi.org/10.1101/2021.03.04.21252913>

- [Pre-print, not peer-reviewed] A community-based, home-collected, longitudinal serosurvey of 290 participants before and after vaccination with either the Moderna or Pfizer/BioNTech vaccines found that a prior outpatient COVID-19 diagnosis was associated with strong anti-spike RBD IgG and in vitro neutralizing responses after one vaccine dose. Median IgG concentration and percent neutralization after one dose were each significantly higher among seropositive individuals who reported prior COVID-19 diagnosis (median 47.7 ug/ml, IgG; >99.9% neutralization) compared to those who were seropositive with no history of diagnostic testing (3.4 ug/ml IgG; 62.8% neutralization) and those who were seronegative (2.2 ug/ml IgG; 39.5% neutralization). The latter two groups reached >95% neutralization after the second dose.

Müller et al. (Mar 5, 2021). Age-Dependent Immune Response to the BioNtech-Pfizer BNT162b2 COVID-19 Vaccination. Pre-print downloaded Mar 5 from <https://doi.org/10.1101/2021.03.03.21251066>

- [Pre-print, not peer-reviewed] Among 176 participants receiving two doses of the Pfizer-BioNTech vaccine in a cohort study in Germany, participants aged >80 years had lower SARS-CoV-2 specific IgG antibody titers and neutralizing titers compared to participants aged <60 years after each dose. While the IgG titer increase between the first and second dose was larger among older participants, mean IgG titers 17 days after the second dose were much lower compared to younger participants. The neutralizing antibody response was similarly lower in older recipients, with only 69% of older participants having detectable neutralizing antibody titers 17 days after the second dose, compared to 98% of younger participants.

Bernal et al. (Mar 2, 2021). Early Effectiveness of COVID-19 Vaccination with BNT162b2 MRNA Vaccine and ChAdOx1 Adenovirus Vector Vaccine on Symptomatic Disease Hospitalisations and Mortality in Older Adults in England. Pre-print downloaded Mar 3 from <https://doi.org/10.1101/2021.03.01.21252652>

- [Pre-print, not peer-reviewed] A study of the real-world effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines in the UK indicated that vaccination with a single dose of either

vaccine was associated with a significant reduction in symptomatic COVID-19 cases in older adults, with strong protection against severe disease. Effects of the Pfizer-BioNTech vaccine among adults 80 and older were observed 10-13 days after vaccination, reaching an effectiveness of 70% from 28-34 days. From 14 days after the second dose, vaccine efficacy was 89%. For those 70 and older, vaccine effectiveness reached 61% from 28-34 days after vaccination. With the Oxford-AstraZeneca vaccine, vaccine effects were seen from 14-20 days after vaccination, efficacy was 60% from 28-34 days, and increased to 73% from day 35 onwards.

Baird et al. (Mar 2, 2021). SARS-CoV-2 Antibodies Detected in Human Breast Milk Post-Vaccination. Pre-print downloaded Mar 3 from <https://doi.org/10.1101/2021.02.23.21252328>

- [Pre-print, not peer-reviewed] Significantly elevated levels of SARS-CoV-2 specific IgG and IgA antibodies were observed in breast milk starting 7 days after the initial vaccine dose in a cohort study of six lactating women who had received both doses of either the Pfizer/BioNTech or Moderna vaccines. The authors note that the response following vaccination was IgG dominant, in contrast to natural infection in which other studies have found IgA predominates.

Lipsitch and Kahn. (Feb 28, 2021). Interpreting Vaccine Efficacy Trial Results for Infection and Transmission. Pre-print downloaded Mar 1 from <https://doi.org/10.1101/2021.02.25.21252415>

- [Pre-print, not peer-reviewed] In simulations of randomized trials to estimate the effect of vaccination on transmission, one dose of the Moderna vaccine reduced the potential for transmission by at least 61%. The analysis suggested that the impact of a given vaccine on viral positivity should be assessed separately in symptomatic individuals and positive test results obtained cross-sectionally, regardless of symptoms. The approach also suggested that the odds ratio of carriage for vaccine vs. placebo can provide an unbiased estimate of vaccine effectiveness against viral positivity, under certain assumptions, and provide a lower bound for transmissibility.

Saul et al. (Mar 1, 2021). Reanalysis of the Pfizer mRNA BNT162b2 SARS-CoV-2 Vaccine Data Fails to Find Any Increased Efficacy Following the Boost Implications for Vaccination Policy and Our Understanding of the Mode of Action. Pre-print downloaded Mar 1 from <https://doi.org/10.1101/2021.02.23.21252315>

- [Pre-print, not peer-reviewed] A study exploring the timing of protection conferred by the Pfizer-BioNTech vaccine indicated that the vaccine was effective beginning 11 days following the first dose, suggesting that vaccine protection precedes the full development of neutralizing antibodies. In addition, efficacy did not increase following the second dose (compared to the period between day 11 and 28).

Manisty et al. (Feb 26, 2021). Antibody Response to First BNT162b2 Dose in Previously SARS-CoV-2-Infected Individuals. The Lancet. [https://doi.org/10.1016/S0140-6736\(21\)00501-8](https://doi.org/10.1016/S0140-6736(21)00501-8)

- A nested case-control study of 51 health care workers found that anti-S titers 19-29 days after the first dose of the Pfizer-BioNTech vaccine were comparable to peak titers after natural infection. Among those with a previous SARS-CoV-2 infection, vaccination increased anti-S titers more than 140-fold from peak pre-vaccine levels. Prior infection was determined by positive detection of antibodies against the SARS-CoV-2 nucleocapsid or the receptor binding domain of the SARS-CoV-2 S1 subunit of the spike protein.

Prendecki et al. (Feb 26, 2021). Effect of Previous SARS-CoV-2 Infection on Humoral and T-Cell Responses to Single-Dose BNT162b2 Vaccine. The Lancet. [https://doi.org/10.1016/S0140-6736\(21\)00502-X](https://doi.org/10.1016/S0140-6736(21)00502-X)

- Individuals with prior SARS-CoV-2 infection generated strong humoral and cellular responses following a single dose of the Pfizer-BioNTech vaccine, according to an analysis of specimens from healthcare workers in the UK (n = 72). Individuals who had not been previously infected showed weaker T-cell responses and generated lower neutralizing antibody titers (median 615.1 vs. 16353 arbitrary units [AU]/mL). Using a T-cell enzyme-linked immunospot assay, vaccine recipients with evidence of prior infection at baseline (n=21) were found to have strong T-cell responses to spike peptides, whereas responses were significantly weaker among infection-naïve vaccine recipients (n=30). 24 (50%) of 48 all recipients generated responses that could be considered negative.

Romero-Brufau et al. (Feb 26, 2021). *The Public Health Impact of Delaying a Second Dose of the BNT162b2 or MRNA-1273 COVID-19 Vaccine*. Pre-print downloaded Feb 26 from <https://doi.org/10.1101/2021.02.23.21252299>

- [Pre-print, not peer-reviewed] An agent-based model estimated the impact of a strategy of delaying a second COVID-19 vaccine dose on cumulative mortality and found that a delayed second dose approach could result in reduced cumulative mortality under certain conditions, particularly in people under 65 years of age. The model was constructed using a simulated population of 100,000 agents based on a real-world US county. It predicted both a reduction in total mortality and cumulative infections at assuming and 80% and 90% first dose efficacy, resulting in absolute cumulative mortality reductions between 26 and 47 deaths per 100,000 population. The model also suggested that a delayed second dose for people under 65 years of age is optimal, assuming a first-dose efficacy of 80% and for vaccination rates at or below 0.3% population per day. The conditions in which these reductions were observed included the first dose efficacy being above 70% and vaccination rates remaining below 1% of the population per day.

Pellini et al. (Feb 26, 2021). *Obesity May Hamper SARS-CoV-2 Vaccine Immunogenicity*. Pre-print downloaded Feb 26 from <https://doi.org/10.1101/2021.02.24.21251664>

- [pre-print; not peer-reviewed] Antibody titers two weeks after receiving a second dose of the Pfizer-BioNTech vaccine were lower in obese healthcare workers (BMI >30), after adjusting for age. 99.5% of the 248 participants developed a humoral immune response after vaccination, and antibody titers were higher in younger people and in women. The authors note that the importance of the magnitude of a humoral response is still under investigation.

Rinott et al. (Feb 26, 2021). *Reduction in COVID-19 Patients Requiring Mechanical Ventilation Following Implementation of a National COVID-19 Vaccination Program — Israel, December 2020–February 2021*. *MMWR*. <https://doi.org/10.15585/mmwr.mm7009e3>

- In Israel, the ratio of COVID-19 patients over the age of 70 requiring mechanical ventilation declined 67% compared to those under 50 from October–December 2020 to February 2021 after a national immunization program resulting in a 2-dose vaccination coverage of 84% among people over the age of 70. The authors suggest that this provides preliminary evidence that the nationwide vaccination campaign has been effective in reducing severe COVID-19 requiring mechanical ventilation.

Dagan et al. (Feb 24, 2021). *BNT162b2 MRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting*. *New England Journal of Medicine*. <https://doi.org/10.1056/NEJMoa2101765>

- In an observational study of the mass vaccination campaigns in Israel, real world effectiveness of the Pfizer vaccine 7 or more days after the second dose was 92% for documented SARS-CoV-2 infection, 94% for symptomatic infection, 87% for hospitalization, and 92% for severe disease. The study included 596,618 individuals matched to unvaccinated controls in a 1:1 ratio according to demographic and clinical characteristics.
- Vaccine effectiveness between 14 and 20 days after the first dose was 46%, 57%, 74%, 62%, and 72% in preventing any documented SARS-CoV-2 infection, symptomatic infection, hospitalization, severe disease, and death, respectively.
- The estimated vaccine effectiveness in preventing any infection among studied sub-populations was consistent across age groups, with potentially lower effectiveness in individuals with multiple co-existing conditions.

Safety Monitoring

Blumenthal et al. (Mar 8, 2021). Acute Allergic Reactions to MRNA COVID-19 Vaccines. JAMA. <https://doi.org/10.1001/jama.2021.3976>

- Among employees of Mass General Brigham (MGB), a Boston-based hospital and physicians network, who received their first dose of either the Pfizer-BioNTech or Moderna vaccine (n=64,900), acute allergic reactions of any type were reported by 1,365 employees overall (2.1%) and anaphylaxis was reported by 16 employees (2.5 cases per 10,000 vaccinations).. Among those reporting anaphylaxis, 63% had a prior allergy history and 31% had a history of anaphylaxis.

Blumenthal et al. (Mar 3, 2021). Delayed Large Local Reactions to MRNA-1273 Vaccine against SARS-CoV-2. New England Journal of Medicine. <https://doi.org/10.1056/NEJMc2102131>

- A case series of 12 patients reported delayed large local reactions (skin redness, tenderness and swelling) in response to the Moderna vaccine within 4 to 11 days (median 8 days) after the first dose. In all cases, the reactions appeared near the injection site after complete resolution of the initial local and systemic symptoms associated with vaccination. 5 of the 12 reactions were 10 cm or larger in diameter. Most patients received treatment, and symptoms resolved within 2 to 11 days of onset (median 6 days). After receiving the second vaccine dose, 3 patients had recurrent reactions similar to the reaction after the first dose and 3 patients had lower grade reactions.

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

Impact of Vaccinations on COVID-19 Disease and Community Transmission

Levine-Tiefenbrun et al. (Mar 29, 2021). Initial Report of Decreased SARS-CoV-2 Viral Load after Inoculation with the BNT162b2 Vaccine. Nature Medicine. <https://doi.org/10.1038/s41591-021-01316-7>

- In a real-world analysis of data from individuals in Israel who tested positive for SARS-CoV-2 after receiving the first dose of the Pfizer-BioNTech vaccination (n=4,938), viral load was substantially lower (2.8 to 4.5-fold lower) for infections occurring 12-37 days after the first dose compared to individuals who had not been vaccinated. Cycle of threshold (Ct) values for the *E* gene, *RdRp* gene, *N* gene and the internal control were determined for each positive test. The authors suggest that reduced viral loads may affect viral shedding, contagiousness, and disease severity.

Milman et al. (Mar 29, 2021). SARS-CoV-2 Infection Risk among Unvaccinated Is Negatively Associated with Community-Level Vaccination Rates. Pre-print downloaded Mar 30 from <https://doi.org/10.1101/2021.03.26.21254394>

- [Pre-print, not peer-reviewed] Increases in the proportion of individuals aged 16-50 years receiving the first dose of the Pfizer-BioNTech vaccine were followed by declines in the SARS-CoV-2 positivity rate among a bystander unvaccinated cohort of people under 16 years old in 223 geographically defined communities in Israel. The proportion of vaccinated individuals and SARS-CoV-2 positivity rate of the unvaccinated cohort was measured at three different intervals between January and March 2021, with a 35-day delay in between to allow for the immunization effects of the vaccine to take effect. A strong negative correlation was observed when comparing the change in proportions of individuals vaccinated to the change in positivity rate of the unvaccinated cohort. While

communities included in the study had a low pre-vaccination community-level positivity rate (3.6%), the authors note that decline in the SARS-CoV-2 positivity rate among the bystander unvaccinated cohort could be affected by acquired immunity from prior infection, as well as individual behavior and public policy guidelines.

Saad-Roy et al. (Mar 9, 2021). *Epidemiological and Evolutionary Considerations of SARS-CoV-2 Vaccine Dosing Regimes*. *Science*. <https://doi.org/10.1126/science.abg8663>

- An immuno-epidemiological model suggests that a one-dose vaccination strategy would likely decrease short-term SARS-CoV-2 infections. Long-term outcomes, as well as likelihood of viral evolution driven by partial immunity, are mainly driven by relative immune robustness of one versus two doses. [EDITORIAL NOTE: A pre-print related to this manuscript was summarized on February 4, 2020]

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

Trial and real world evidence involving variants of concern

Emary et al. (Mar 30, 2021). *Efficacy of ChAdOx1 NCoV-19 (AZD1222) Vaccine against SARS-CoV-2 Variant of Concern 202012/01 (B.1.1.7): An Exploratory Analysis of a Randomised Controlled Trial*. *The Lancet*. [https://doi.org/10.1016/S0140-6736\(21\)00628-0](https://doi.org/10.1016/S0140-6736(21)00628-0)

- Post-hoc analysis of the Oxford-AstraZeneca vaccine indicated that clinical vaccine efficacy against symptomatic, PCR-positive infection was 70.4% for the B.1.1.7 variant and 81.5% for non-B.1.1.7 lineages (not including the B.1.351 variant). Neutralization activity via vaccine-induced antibodies *in vitro* was also lower against the B.1.1.7 variant (geometric mean ratio 8.9). Participants 18 and older in efficacy cohorts (n=8534) were included in the analysis, and received either the COVID-19 vaccine or a control meningococcal conjugate vaccine. [EDITORIAL NOTE: This paper was summarized as a pre-print on February 5, 2021]

Madhi et al. (Mar 16, 2021). *Efficacy of the ChAdOx1 NCoV-19 Covid-19 Vaccine against the B.1.351 Variant*. *New England Journal of Medicine*. <https://doi.org/10.1056/NEJMoa2102214>

- Two doses of the Oxford-AstraZeneca (ChAdOx1 nCoV-19) vaccine did not show protection against mild-to-moderate COVID-19 among people infected with the B.1.351 variant in a multicenter randomized trial in South Africa. Mild-to-moderate COVID-19 developed in 23 of 717 placebo recipients (3.2%) and in 19 of 750 vaccine recipients (2.5%), for an efficacy of 21.9%. Among the 42 participants who developed COVID-19, 39 (92.9%) were infected with the B.1.351 variant. Vaccine efficacy against this variant, analyzed as a secondary end point, was 10.4%. The authors note that the demographic profile of enrolled participants contributed to the lack of severe COVID-19, and therefore trial results are inconclusive regarding the vaccine's potential to protect against severe disease. [EDITORIAL NOTE: A pre-print related to this manuscript was summarized on February 12, 2020]

Shinde et al. (Mar 3, 2021). *Preliminary Efficacy of the NVX-CoV2373 Covid-19 Vaccine Against the B.1.351 Variant*. Pre-print downloaded Mar 3 from <https://doi.org/10.1101/2021.02.25.21252477>

- *[Pre-print, not peer-reviewed]* Results from a multicenter, randomized, observer-blinded, placebo-controlled trial in South Africa of the NVX-CoV2373 (Novavax) nanoparticle vaccine indicated that among 2,684 participants who were SARS-CoV-2 seronegative at baseline (94% HIV-negative; 6% people living with HIV), vaccine efficacy was 49.4%, with 15 and 29 predominantly mild to moderate COVID-19 cases in vaccine and placebo recipients, respectively. Efficacy in HIV-negative participants was 60.1% and did not differ by baseline SARS-CoV-2 serostatus. Of the primary endpoint COVID-19 cases with available whole genome sequencing, 38 (92.7%) of 41 were the B.1.351 variant.
- One notable finding from the study was that among placebo recipients, the incidence of symptomatic COVID-19 was similar in those with and without evidence of antibodies against SARS-CoV-2 at baseline during the first 2 months of follow-up (5.3% vs 5.2%). The authors conclude that this suggests prior infection provided no protection against developing clinical disease when infected with the B.1.351 variant.

***In vitro* evidence**

Zhou et al. (Mar 24, 2021). B.1.526 SARS-CoV-2 Variants Identified in New York City Are Neutralized by Vaccine-Elicited and Therapeutic Monoclonal Antibodies. Pre-print downloaded Mar 25 from <https://doi.org/10.1101/2021.03.24.436620>

- *[Pre-print, not peer-reviewed]* Neutralizing activity elicited by prior SARS-CoV-2 infection, mRNA vaccines (Pfizer-BioNTech and Moderna), or the Regeneron monoclonal antibody cocktail (REGN10933 and REGN10987) were similar against the B.1.526 variant with the S477N mutation compared to the widely circulating strain with the D614G mutation. In contrast, similar to other E484K harboring variants, the B.1.526 variant with the E484K mutation reduced neutralizing titers of sera from convalescent and vaccinated individuals by nearly 4-fold. REGN10933 alone had a 12-fold reduction in neutralizing activity, but the combined Regeneron cocktail was able to neutralize the B.1.526 E484K variant. Both versions of the B.1.526 variant (S477N mutation and E484K mutation) were first identified in New York City in November 2020, and rapidly spread to account for 12% of detected genomes by mid-February 2021.

Supasa et al. (Feb 18, 2021). Reduced Neutralization of SARS-CoV-2 B.1.1.7 Variant by Convalescent and Vaccine Sera. Cell. <https://doi.org/10.1016/j.cell.2021.02.033>

- The B.1.1.7 variant has a 7-fold higher binding affinity to the angiotensin converting enzyme-2 (ACE2) receptor in human cells than a parent SARS-CoV-2 strain isolated from Wuhan, suggesting a mechanism for the rapid emergence of this variant. Serum from individuals vaccinated with either the Pfizer-BioNTech or the Oxford-AstraZeneca and serum recovered from infection with the Wuhan strain, had only a modest 2-3-fold reduction in neutralization titers against the B.1.1.7 variant. Sera obtained from B.1.1.7-infected individuals show no reduction in titers against the parent strain compared to the B.1.1.7 variant.

Edara et al. (Mar 19, 2021). Neutralizing Antibodies Against SARS-CoV-2 Variants After Infection and Vaccination. JAMA. <https://doi.org/10.1001/jama.2021.4388>

- Neutralizing antibody activity against four SARS-CoV-2 variants, including B.1, B.1.1.7, and N501Y was maintain in sera from individuals with infection- and vaccine-induced antibodies. There was minimal reductions in serum neutralization observed across four representative SARS-CoV-2 strains. Serum was obtained from adults (n=20) hospitalized with COVID-19 5 to 19 days after symptom

onset, convalescent individuals (n=2) 32 to 94 days after symptom onset, and individuals (n=14) 14 days after the 2nd dose in the Moderna vaccine phase 1 clinical trial. Neutralizing activity was evaluated by “live virus focus reduction neutralization tests” against the A.1 lineage similar to original Wuhan strain, the B.1 lineage containing the D614G mutation that has emerged worldwide, the B.1.1.7 variant originally identified in the UK, and the N501Y engineered variant containing mutation in spike protein present across multiple emerging variants. Neutralizing activity was not significantly different across the four variants for both hospitalized COVID-19 patients and convalescent individuals. Neutralizing activity induced by vaccines was reduced for all strains compared to the original A1 strain but was similar for the B.1, B.1.1.7, and synthetic N501Y strain.

Chang et al. (Mar 15, 2021). BNT162b2 mRNA COVID-19 Vaccine Induces Antibodies of Broader Cross-Reactivity than Natural Infection but Recognition of Mutant Viruses Is up to 10-Fold Reduced. Pre-print downloaded Mar 16 from <https://doi.org/10.1101/2021.03.13.435222>

- [Pre-print, not peer-reviewed] Antibodies induced by the Pfizer-BioNTech vaccine had higher binding capacities (avidity) than antibodies induced by natural infection against the receptor binding domain (RBD) containing mutations representative of circulating SARS-CoV-2 variants of concern (N501Y, K417N, E484K, and a combination of all three). Vaccine-induced sera (n=6) reduced binding against the RBD containing the N501Y and K417 mutations (2.5-3 fold reduction) compared to wild type RBD. Of note, both the RBD with E484K mutation and RBD with all three mutations reduced binding by ~10-fold, indicating that E484K mutation (found in the B.1.351 and P.1 variant but not in the B.1.1.7 variant) substantially reduces antibody binding.

Dejnirattisai et al. Antibody Evasion by the Brazilian P.1 Strain of SARS-CoV-2. Pre-print downloaded Mar 16 from <https://doi.org/10.1101/2021.03.12.435194>

- [Pre-print, not peer-reviewed] The SARS-CoV-2 P.1 variant, which has caused large outbreaks in Brazil, is less resistant to neutralization from both convalescent serum and vaccine-induced serum than the B.1.351 variant originally identified in South Africa, despite containing similar receptor binding domain (RBD) mutations (E484K, K417N/T and N501Y). Similar to the B.1.351 variant, mutations associated with the P1 variant completely abrogated the binding of multiple neutralizing antibodies directed against the RBD, including a variety of antibodies currently in development for therapeutic use. In contrast, the reduction in neutralization activity of convalescent plasma from recovered volunteers against the P.1 variant was only modest (~3-fold reduction versus the ancestral Victoria strain) when compared to the reduction in neutralization observed with B.1.351 variant (~13-fold reduction versus the Victoria strain). Sera from recipients of either the Pfizer-BioNTech or Oxford-AztraZeneca vaccine had similar modest reductions in neutralization activity (~3-fold) when compared to the reductions in neutralization observed with the B.1.351 variant (~8-9 fold).

Fisher et al. (Mar 11, 2021). ChAdOx1 nCoV-19 (AZD1222) protects against SARS-CoV-2 B.1.351 and B.1.1.7. Pre-print downloaded Mar 12 from <https://doi.org/10.1101/2021.03.11.435000>

- [Pre-print, not peer-reviewed] An investigation of the Oxford-AstraZeneca (ChAdOx1 nCoV-1; AZD1222) vaccine efficacy against SARS-CoV-2 variants of concern B.1.1.7 and B.1.351 in Syrian hamsters showed a 9.5-fold reduction of virus neutralizing antibody titer in vaccinated hamster sera

against B.1.351 compared to B.1.1.7. Vaccinated hamsters challenged with B.1.1.7 or B.1.351 did not lose weight compared to control animals.

- Histopathological evaluation showed extensive pulmonary pathology caused by B.1.1.7 or B.1.351 replication in the control animals, but none in the vaccinated animals. No infectious virus and minimal to no viral subgenomic RNA (sgRNA) was detected in lungs of vaccinated animals.

Becker et al. (Mar 10, 2021). Immune Response to SARS-CoV-2 Variants of Concern in Vaccinated Individuals. Pre-print downloaded Mar 11 from <https://doi.org/10.1101/2021.03.08.21252958>

- [Pre-print, not peer-reviewed] Sera from both individuals with prior SARS-CoV-2 infection (n=35) and individuals fully vaccinated with the Pfizer-BioNTech vaccine (n=23) showed nearly identical antibody binding responses against the B.1.1.7 Cluster 5 and CAL.20C variants compared to wild-type SARS-CoV-2. In contrast, both binding and neutralizing antibody responses among vaccinated individuals were diminished against the B.1.351 variant compared to wild-type SARS-CoV-2, although the 2nd vaccine dose appeared to confer increased neutralization capacities. In a separate analysis, the authors found that individuals with prior SARS-CoV-2 infection had higher IgA antibody titers in saliva, while vaccinated individuals had high IgG titers.

Trinite et al. (Mar 5, 2021). Previous SARS-CoV-2 Infection Increases B.1.1.7 Cross-Neutralization by Vaccinated Individuals. Pre-print downloaded Mar 10 from <https://doi.org/10.1101/2021.03.05.433800>

- [Pre-print, not peer-reviewed] Sera from individuals who had been previously infected with SARS-CoV-2 and received the vaccine showed equivalent neutralizing responses against the B.1.1.7 variant and original virus strain, while sera from vaccinated individuals with no prior infection showed reduced neutralization against B.1.1.7. Neutralizing activity was assessed against pseudoviruses bearing the spike protein from the original strain or that of the D614G or B.1.1.7 variants.

Amanat et al. (Mar 9, 2021). The Plasmablast Response to SARS-CoV-2 mRNA Vaccination Is Dominated by Non-Neutralizing Antibodies That Target Both the NTD and the RBD. Pre-print downloaded Mar 10 from <https://doi.org/10.1101/2021.03.07.21253098>

- [Pre-print, not peer-reviewed] A study of vaccine-induced polyclonal antibodies and monoclonal antibodies (mAbs) from subjects who received SARS-CoV-2 mRNA vaccines found that polyclonal antibody responses were robust and comparable to or exceeded those observed after natural infection. However, most vaccine-induced mAbs did not demonstrate neutralizing activity. Neutralizing activity of N-terminal domain (NTD) mAbs, but not receptor binding domain (RBD) mAbs, against a virus carrying the E484K substitution and extensive changes in the NTD was abolished, which the authors indicate suggests that some vaccine-induced RBD-binding antibodies may protect against viral variants carrying E484K.

Chen et al. (Mar 4, 2021). Resistance of SARS-CoV-2 Variants to Neutralization by Monoclonal and Serum-Derived Polyclonal Antibodies. Nature Medicine. <https://doi.org/10.1038/s41591-021-01294-w>

- Most convalescent sera from people who had recovered from mild COVID-19 (n=29) and virtually all Pfizer-BioNTech mRNA vaccine-induced immune sera (n=24) 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*. [EDITORIAL NOTE: A Pre-print related to this manuscript was summarized on January 17, 2021]

- [Pre-print, not peer-reviewed] Reduced neutralization titers against the P.1 SARS-CoV-2 variant were found in both convalescent plasma (6.5-fold) and plasma from individuals who received an mRNA vaccine (2.2-2.8-fold). The P.1 variant completely resisted neutralization by multiple neutralizing monoclonal antibodies. Using a VSV-based SARS-CoV-2 pseudovirus with all 10 mutations of the P.1 variant, the authors note that the magnitude of the loss of activity from vaccinated individuals against this variant was modest relative to that observed with the B.1.351 variant.

Wang et al. (Mar 2, 2021). *Increased Resistance of SARS-CoV-2 Variant P.1 to Antibody Neutralization*. Pre-print downloaded Mar 3 from <https://doi.org/10.1101/2021.03.01.433466>

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.1.351 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

Moderna Vaccine

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

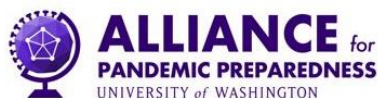
Polack et al. (Dec 10, 2020). *Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine*. *New England Journal of Medicine*. <https://doi.org/10.1056/NEJMoa2034577>

- 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 $\geq 38^{\circ}\text{C}$) 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



Updated 4/2/2021

FDA. (Feb 26, 2021). Janssen Ad26.COVS 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.COVS 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

Novavax. (Mar 11, 2021). Novavax Confirms High Levels of Efficacy Against Original and Variant COVID-19 Strains in United Kingdom and South Africa Trials. Downloaded Mar 11 from <https://ir.novavax.com/news-releases/news-release-details/novavax-confirms-high-levels-efficacy-against-original-and>

- [Press release, not peer-reviewed] A Phase 3 trial of the Novavax vaccine (NVX-CoV2373) in the UK indicated an efficacy of 96.4% against mild, moderate and severe disease caused by the original COVID-19 strain. The company also announced final results of its Phase 2b trial conducted in South Africa, with an efficacy of 55.4% among HIV-negative trial participants in a region where the vast majority of strains are B.1.351 variants. Across both trials, NVX-CoV2373 demonstrated 100% protection against severe disease, including all hospitalization and death.

Vaccines Authorized for Use Outside the US

Oxford-AstraZeneca vaccine

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](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](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)

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](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.

Sinovac: CoronaVac

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](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.

Other Candidate Vaccines

Bharat Biotech whole-virion inactivated SARS-CoV-2 vaccine

Ella et al. (Mar 8, 2021). *Safety and Immunogenicity of an Inactivated SARS-CoV-2 Vaccine, BBV152: Interim Results from a Double-Blind, Randomised, Multicentre, Phase 2 Trial, and 3-Month Follow-up of a Double-Blind, Randomised Phase 1 Trial. The Lancet Infectious Diseases.* [https://doi.org/10.1016/S1473-3099\(21\)00070-0](https://doi.org/10.1016/S1473-3099(21)00070-0)

- Interim results from a double-blind randomized phase 2 trial ($n=380$) of the Bharat Biotech whole-virion inactivated SARS-CoV-2 vaccine (BBV152) show robust neutralizing titers against wild-type SARS-CoV-2 at day 56 following two doses administered on day 0 and day 28. In a plaque-reduction neutralization test, the 6 μg dose group compared to the 3 μg dose group had higher geometric mean neutralizing titers (197 vs 100) and higher proportion of seroconversion (98% vs 93%) at day 56. No significant difference was observed in the proportion of participants who reported local or systematic adverse reactions between the dose groups (20% vs 21%), and no serious adverse events were reported in the study.

Additional Trials in Populations of Interest

Persons with prior COVID Infection

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.

Vaccine Uptake and Acceptance

Stern et al. (Apr 2, 2021). *Willingness to Receive a COVID-19 Vaccination Among Incarcerated or Detained Persons in Correctional and Detention Facilities — Four States, September–December 2020*.

MMWR. <https://doi.org/10.15585/mmwr.mm7013a3>

- The COVID-19 vaccination refusal rate was 45% among 5,110 surveyed residents of three prisons and 13 jails across four states during September to December 2020 (all three prisons and 10 jails in Washington State). The most common reason for vaccination refusal was distrust of health care, correctional, or government personnel or institutions (20%). 10% of surveyed residents expressed vaccine hesitancy; waiting for more information was the most common reason for hesitancy (55%). Willingness to be vaccinated was lowest among Black participants (37%; 510 of 1,390), participants aged 18–29 years (39%; 583 of 1,516), and those who lived in jails versus prisons (44%; 1,850 of 4,232).

Grumbach et al. (Mar 30, 2021). Association of Race/Ethnicity With Likelihood of COVID-19 Vaccine Uptake Among Health Workers and the General Population in the San Francisco Bay Area. *JAMA Internal Medicine*. <https://doi.org/10.1001/jamainternmed.2021.1445>

- Black, Latinx, and Asian employees of three large medical centers in San Francisco had lower odds of reporting that they were likely to get vaccinated against COVID-19 compared to white employees in a cross-sectional study conducted from November 2020 to January 2021 (n=1,803). Compared to white respondents, Black, Asian and Latinx had 50%, 63%, and 72% lower odds for likelihood of vaccine uptake, respectively. Similarly, ethnic minorities in a general population cohort (n=3,161) residing in counties in the San Francisco Bay Area reported lower odds for likelihood of vaccine uptake compared to white respondents. While ratings of reasons to get vaccinated were similar across racial/ethnic groups, minorities were significantly more likely than white respondents to endorse reasons not to get vaccinated, such as less confidence in vaccine efficacy, less trust in vaccine manufacturers, and more worry that government process were rushed.

Lindemer et al. (Mar 26, 2021). Counties with Lower Insurance Coverage Are Associated with Both Slower Vaccine Rollout and Higher COVID-19 Incidence across the United States. Pre-print downloaded Mar 29 from <https://doi.org/10.1101/2021.03.24.21254270>

- [Pre-print, not peer-reviewed] US counties with high levels of uninsured individuals had significantly lower COVID-19 vaccination rates and tended to have the highest COVID-19 incidence rates in March 2021 relative to December 2020, according to an analysis of data from over 1,500 counties (228 million individuals). Counties with higher percentages of Black and Hispanic individuals also had significantly lower vaccination rates, and smaller declines in COVID-incidence rates.

Kriss et al. (Mar 15, 2021). COVID-19 Vaccine Second-Dose Completion and Interval Between First and Second Doses Among Vaccinated Persons — United States, December 14, 2020-February 14, 2021. *MMWR*. <https://doi.org/10.15585/mmwr.mm7011e2>

- Vaccination data reported to CDC indicate that among people who received the first dose of either the Moderna or Pfizer/BioNTech vaccines as of February 14, 2021, and for whom enough time had elapsed to receive the second dose, 88.0% had completed the series and 8.6% had not received the second dose. Among all people who received 2 doses, 95.6% received the second dose within the recommended time interval (Pfizer-BioNTech 1-25 days and Moderna 24-32 days since the first dose). The percentage of people who missed the second dose varied by geographic area (range = 0.0%–9.1%).

Jain et al. (Mar 12, 2021). A Rapid Review of COVID-19 Vaccine Prioritization in the U.S. Alignment between Federal Guidance and State Practice. Pre-print downloaded Mar 15 from <https://doi.org/10.1101/2021.03.11.21253411>

- [Pre-print, not peer-reviewed] A study assessing variability in vaccine priority groups between state and federal guidance found that while state plans largely prioritized healthcare workers and residents of long-term care facilities (consistent with federal guidelines), essential workers were often excluded from state priority plans. Of 37 states that included frontline essential workers, 12 assigned them to a lower priority than recommended by federal guidance. Almost all states prioritized individuals ages 65-74 years, and most assigned them to a higher position than

recommended in federal guidance. Some groups not considered high priority in federal guidelines, such as people living in congregate settings or with disabilities, were highly prioritized by 38 states.

Chapman et al. (Mar 8, 2021). *Comparison of COVID-19 Vaccine Prioritization Strategies in the United States*. Pre-print downloaded Mar 10 from <https://doi.org/10.1101/2021.03.04.21251264>

- [Pre-print, not peer-reviewed] A static simulation model using California as an example to compare the impact of different vaccine prioritization strategies in the United States found that prioritizing older individuals averted the highest proportion of disability-adjusted life years (DALYs, 40% for 5 million individuals vaccinated) and deaths (65%), but the lowest proportion of cases (12%). Prioritizing essential workers averted the lowest proportion of DALYs (25%) and deaths (33%). Allocating vaccines simultaneously by age and location or multiple factors (age, sex, race/ethnicity, location, occupation, and comorbidity status) averted a significantly higher proportion of DALYs (48% and 56%) than any strategy prioritizing by a single risk factor. The authors note that their approach may underestimate the impact of vaccination by not incorporating onward transmission.