

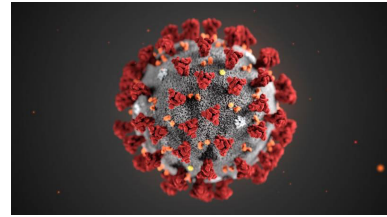
Facts on the Coronavirus

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The Virus

- COVID-19 (SARS-CoV) is one of several coronaviruses: 4 are known to cause the common cold, one was SARS (2004) and the other MERS (2012).
 - SARS is considered contained and MERS is restricted to the Arabian Peninsula; neither have a vaccine.
 - They are far less infectious but more fatal (10-50% fatality rate) than the current COVID-19.
- It's called a coronavirus because of the "crown" of protein spikes on the surface
- All coronaviruses are spread through aerosolization and mucus exposure.
- COVID-19 has been shown to last about 4 days on impermeable surfaces and about 2 days on permeable surfaces.
- The virus is a sack of fat with protein spikes on the outside and messenger RNA (mRNA) on the inside.
 - The virus itself is not alive, but the protein spikes attach to the cell it is infecting via the ACE2 (Angiotensin-Converting Enzyme 2) receptor.
 - The ACE2 receptor is a vasodilator that influences blood flow, making it a poor target for treatment or a vaccine.
 - The ACE2 receptor is found all over the body but is prevalent on lung cells lining air sacs, which is why this virus infection can cause pneumonia.
 - Once the virus attaches to the cell via the protein spike, it injects the mRNA into the cell which takes over cellular genetic reproduction, causing the cell to become a virus factory. Eventually the cell bursts and releases additional virus.
 - Mutations have been found on the structure of the protein spike which make the virus more infectious (easier to spread) but not to date more virulent (doesn't cause more or more serious disease).
 - Genetic sequence completed 1/11/2020



Infectivity

- COVID-19 is 3 times more infectious than other respiratory viruses.
- The chances of being exposed depend on how many virus particles you are exposed to and the length of time you are exposed.
 - **Maximum exposure time is only 15 minutes.**
- The infection rate in the US is 15 times that of the rest of the world, and the world is going through Phase 2 – including the US. **We do not have this under control. All 50 states are experiencing spikes higher than previously seen, almost all are showing third wave spikes.**
 - WE ARE NOW AT 1 IN 14 PEOPLE INFECTED IN THE US – IF THE SPIKES CONTINUE, WE MAY BE AT 1 IN 3 BY MARCH. LA is at 1 in 5. There are 2000-3000 deaths per day and 200,000-300,000 new infections per day.
 - Countries that had previously controlled spread are re-experiencing rising infection rates (142 countries). India and Brazil have infection rates similar to the US.
- All ages can be infected. The severity of the symptomatic response is correlated to age and the presence of other underlying medical conditions, but not exclusively.
- All ages are infectious.

- **40% of those who are infected are asymptomatic**, but they are still infectious (they just don't know it and neither do you).
- For those who are infected and will go on to develop symptoms, **they are infectious (more highly infectious) for up to 8 days before symptoms emerge** (so again they don't yet know they are infectious and neither do you- and that could be 2 Sundays).
- A recent study of young children in the US showed that children – who are mostly asymptomatic – have up to **25 times** the amount of virus in the nasal passages than hospitalized adults. They can be significant vectors of community spread. At last count, testing has shown that 40-90% of children in spots are infected.
- Demonstrated cases of re-infection have been documented. It is not known whether the virus becomes latent (stays in the body and re-emerges, similar to chicken pox becoming shingles later in life). The re-infection appears to be a mutated version of the virus, and the second infection brings more significant symptomatology. This means the virus is endemic – it will always be with us – and that eventual vaccines may be annual.
- “exposure” is multiplicative – if you've met with 10 people during the day and they've each met with 10 people, you've been potentially exposed to 100 people

Status

- Currently WHO reports more than 93 million confirmed cases of COVID-19 globally with more than 2.0 million reported deaths
 - More than 217 countries are involved; only two report no current cases (British Virgin Islands and Montserrat)
 - In the US, we have more than 23.5 million confirmed cases and 391,000 deaths
 - A person dies from COVID every 15 seconds (average globally, World Health Organization)
- Two significant mutations have emerged (2021)
 - one in Europe is currently in the US, it is more infectious, not more virulent, and appears to be covered by the current mRNA vaccines
 - one in South Africa is also more infectious but appears to have mutated a critical part of the protein spike that may make it more refractive to mRNA vaccines

Fatality, Co-Morbidity and Long-Term Sequelae

- COVID-19 is **10 times more fatal than the flu** (COVID-19 has an overall 1% fatality rate; the flu is about 0.1%)
- A 1% fatality rate in the US is 3.3 Million people
- Currently in the US 1 person dies about every 70 seconds from COVID; in the EU it's about 1 every 17 seconds
- The fatality rate is generally correlated to age and underlying medical conditions
 - Fatality is 30.5/1000 for 85 years of age and above (3%)
 - Fatality is 6/1000 for 65-84, 4/1000 for 50-64, 1/900 18-29, 0.3/1000 5-17
- The virus affects the respiratory system but also the heart, liver, kidneys, GI tract, central nervous system, pancreas (causing diabetes), thyroid (affecting metabolism), and causes significant clotting in small blood vessels
- The **long-term consequences** are far more significant than other viruses: for every 1 fatality there will be:
 - 19 hospitalizations (62 million)
 - 18 who develop permanent heart damage (in one study, 80% of those who recovered showed heart damage by MRI) (59 million)
 - 10 who develop permanent lung scarring and damage (32 million)

- 3 who develop permanent kidney damage (10 million)
- 3 strokes (10 million)
- 2 permanent neurological defects (up to and including psychoses, especially in younger population) (6.5 million)
- 2 significant cognitive dysfunctions (6.5 million)
- Long-lasting nerve damage, affecting everything from smell to walking

Symptoms

- Early cardinal symptoms include loss of taste and smell, fatigue, shortness of breath, fever, dry cough, joint pain, heaviness in the chest; Progressive symptoms include acute respiratory failure, sepsis, intravascular coagulation (blood clots), and multi-organ failure
- Symptoms are long-lasting – 3 months' post recovery only about 12% are symptom-free, and symptoms can recur after abating
- Stillbirths with infection have been reported to be as high as 80% of pregnancies

Treatments

- There are very few significantly effective treatments for COVID-19
- Normal flu treatments (neuraminidase and endonuclease inhibitors) do not work on COVID-19
- Early in the infection treatment with an anti-viral (Remdesivir) showed some promise; later (smaller studies) have called that into question. Remdesivir just approved by FDA for COVID (10/20); the only approved treatment
- Later in the infection, to stem a hyper-immune response and cytokine storm (causing significant inflammation in the body, the cause of some of the long-term consequences), anti-inflammatory agents (Dexamethasone, a steroid) have been shown to be marginally useful
- Convalescent plasma has also shown some promise but has not been sufficiently tested to demonstrate proof. FDA has not approved convalescent plasma for treatment.
- Some physical manipulation, such as lying the patient on their stomach instead of their back, has provided some relief of lung damage
- Studies with monoclonal antibodies for treatment and potentially prevention are underway (Regeneron has one in trials with the NIH; this approach has been shown to be effective for Ebola)

Immunity

- The native immune response to COVID-19 has generally been shown to be weak and short-lived
- T-cell response (one of the types of normal immune cells in the body) to the virus may be a more important measure of immunity than antibody formation and duration, however, tests for antibody are quick and inexpensive, whereas testing for T-cell response is difficult and expensive
- Currently there have been antibodies demonstrated 3-4 months after infection
- Documented re-infections show that native immunity is too specific to cover mutations

Vaccines

- There are currently almost 200 vaccines in various stages of testing (164 pre-clinical, 64 Phase 1, 17 Phase 2, 8 Phase 3)
- Eight vaccine candidates are currently in Phase III (large-scale human) testing
 - Two utilize an mRNA technology, using snippets of the coronavirus mRNA that will infect but not cause disease, to prime the immune system into recognizing the virus and providing early immunity (Moderna and Pfizer)
 - both vaccines have been shown to be highly effective (95%) but it is not known how long that protection lasts and there is not long term safety data yet

- mRNA vaccines have never been commercialized in the US and require extreme transport and storage conditions (up to -70° F), making them difficult to use and requiring some additional safety information for review and approval
- both have been approved by FDA and the EU board of health for emergency approval and are beginning to be rolled out per CDC guidelines
- initial side effects are generally mild flu-like symptoms; anaphylaxis is rare but under evaluation
- takes 2-4 weeks for immunity to develop – can still be infected during that time
- boosters 3-4 weeks apart to get to full immunity potential
- These manufacturers have promised all safety data will be available to consumers
- These are showing results similar to the antibody and T-cell responses after recovery from the virus (similar to the body's response)
- The early vaccine data shows that the vaccine appears as effective in older patients as in younger (not true for all vaccines).
- Other vaccines are using traditional vaccine manufacture processes, similar to the vaccines on the market today
 - These will be easier to transport/store globally
 - Astra-Zeneca and Janssen have completed Phase III and will soon petition FDA for EUA; AZ vaccine is approved in the UK
 - Novavax entering Ph III
 - These are showing results similar to the antibody and T-cell responses after recovery from the virus (similar to the body's response)
 - Others from known US pharma companies known for vaccine development – GlaxoSmithKline and Merck – are in Phase II/III clinical trials

Platform	Attributes	Doses	Vaccine Candidate (Manufacturer)
mRNA	Fast development speed; low- to-medium manufacturing scale	2	BNT-162b2 (Pfizer, BioNTech); mRNA-1273 (Moderna)
DNA	Fast development speed; medium manufacturing scale	2	INO-4800 (Inovio)
Viral vector	Medium development; high manufacturing scale	1 or 2	AZA-1222 Ad5-CoV (AstraZeneca; Oxford University); Ad26.COVS.2.S (Johnson & Johnson)
Protein subunit	Medium- to-fast development; high manufacturing scale	2	NVX-CoV2373 (Novavax)

- Many manufacturers are taking a risk and beginning to produce stockpiles of the vaccines before approval to be ready as early as possible
- Manufacturers and scientists are also engaged in an unprecedented open-source data share
- **Vaccine rollout is slower than anticipated in the US**
 - First vaccinations will go to first responders, health care workers, those at highest risk
 - The majority of the population will not likely be vaccinated before the middle of next year (June-August)
 - Current surveys show that 50% of Americans say they will NOT get the vaccine
 - **Only vaccinations will protect – simply having the vaccine and expecting others to be vaccinated will not provide epidemiologic protection sufficient to stop virus spread**

GET YOUR FLU SHOT THIS YEAR!

Vaccine	Clinical Trials	Results	Regulatory Status
<p>BNT-162b2 (2 injections) Pfizer (nucleoside-modified messenger RNA (modRNA) vaccine that encodes an optimized SARS-CoV-2 receptor-binding domain (RBD) antigen)</p>	<p>Phase 3 trial ongoing in individuals 43000+ 16 y and older, 40% diverse; 40%>55yoa</p> <p>In mid-October 2020, company allowed by FDA to expand phase 3 trial to adolescents 12 y and older.</p>	<p>Primary efficacy analysis: 95% effective against clinically evident COVID-19 infection 28 d after 1st dose across all subgroups ^[9]</p> <p>Well tolerated across all populations ^[9] 170 confirmed cases (placebo group, 162; vaccine group, 8) 10 severe cases after 1st dose (placebo group, 9; vaccine group, 1) ^[9] Efficacy consistent across age, sex, race, and ethnicity ^[9] Not evaluated for asymptomatic infection/carriage ^[9]</p>	<p>First approved in United Kingdom on December 2, 2020 Approved in early December 2020 by Bahrain and Canada Emergency use authorized by FDA on December 11, 2020.</p>
<p>mRNA-1273 (2 injections) Moderna (encodes the S-2P antigen)</p>	<p>US phase 3 trial (COVE) ongoing 30000+, 18yr +; 40% diverse Phase 2/3 trial began in adolescents 12-17 y in December 2020</p>	<p>Primary efficacy analysis: Efficacy rate 94.1% 196 confirmed cases (placebo group, 185; vaccine group, 11) Only severe illness (30 cases) was in placebo group, including 1 death ^[13] 90 d after 2nd dose (30 participants): high levels of binding and neutralizing antibodies that fell but remained elevated Well tolerated ^[10]</p>	<p>Emergency use authorized by FDA on December 18, 2020.</p>

Vaccine	Clinical Trials	Results	Regulatory Status
<p>AZA-1222 (2 injections) AZ-Oxford (replication-deficient chimpanzee adenoviral vector vaccine containing the surface glycoprotein antigen (spike protein) gene. This vaccine primes the immune system by eliciting antibodies to attack the SARS-CoV-2 virus)</p>	<p>Phase 3 trials ongoing. One dosing regimen (n = 2741) showed vaccine efficacy of 90% when given as a half dose, followed by a full dose at least 1 month later. Another dosing regimen (n = 8895) showed 62% efficacy when given as 2 full doses at least 1 month apart. The combined analysis from both dosing regimens (N = 11,636) resulted in an average efficacy of 70.4%. All results were statistically significant (p < .0001). [15] Concerns about the clinical trial implementation and data analysis have emerged because the half-dose regimen was not in the approved study design. [16, 17]</p>	<p>Participant in United Kingdom diagnosed with transverse myelitis, triggering temporary hold on trial. Interim analysis of phase 3 clinical trial in United Kingdom, Brazil, and South Africa: Efficacy 90%, depending on dosage; average efficacy of 70.4% in combined analysis of 2 dosing regimens. 131 COVID-19 cases: from 21 d after 1st dose, 10 hospitalizations, all in placebo group (2 classified as severe; 1 death)</p>	<p>Approved in United Kingdom December 29, 2020.</p> <p>Phase 3 in United States.</p>
<p>Ad26.COV2.S (1 injection) Janssen adenovirus serotype 26 (Ad26) recombinant vector-based vaccine)</p>	<p>Phase 3 trial (ENSEMBLE) ongoing Second phase 3 trial (EMSEMBLE 2) announced November 15, 2020, to study effects of 2 doses</p>	<p>Phase 1/2a study: antibodies to SARS-CoV-2 observed after a single injection 99% were positive for neutralizing antibodies against SARS-CoV-2 at day 29: strong T-cell responses and a T_H1 response were also noted [11]</p>	<p>Rolling biologics license application submitted in Canada and Europe on December 1, 2020.</p>

Vaccine	Clinical Trials	Results	Regulatory Status
<p>NVX-CoV2373 Novovax (recombinant nanoparticle technology from SARS-CoV-2 genetic sequence to generate an antigen derived from the coronavirus spike protein. This is combined with an adjuvant (Matrix-M). Results of preclinical studies showed that it binds efficiently with human receptors targeted by the virus)</p>	<p>Phase 3 trial in United Kingdom concluded enrollment at end of November 2020. US and Mexico phase 3 trial began December 2020.</p>	<p>Phase 1 data showed the adjuvanted vaccine induced neutralization titers in healthy volunteers that exceeded responses in convalescent serum from mostly symptomatic patients with COVID-19. [12]</p>	<p>Phase 3</p>

Other Vaccines in Development

Vaccine	Comments
<p>INO-4800 (Inovio Pharmaceuticals) ^[19]</p> <p>DNA-based, 2-dose vaccine</p>	<p>Stable at room temperature for more than 1 y; frozen shipment not needed; interim results from phase 1 human trial (n = 40): favorable safety and immunogenicity; expanded to include older participants. ^[46]</p> <p>Phase 2/3 trial (INNOVATE) ongoing; phase 2 to evaluate 2-dose regimen (1 mg or 2 mg) vs placebo in 400 participants.</p> <p>Grant from Bill and Melinda Gates Foundation to speed testing and scale up a smart device (Collectra 3PSP) for large-scale intradermal vaccine delivery; company has also received funds from the US Department of Defense.</p>
<p>CVnCoV (CureVac) ^[20]</p> <p>mRNA, 2-dose vaccine</p>	<p>Preliminary data from phase 1 dose-escalating trial: 12-μg dose provided IgG antibody levels similar to convalescent plasma. phase 2b/3 trial enrollment (goal, 35,000 in Europe and Latin America) ongoing.</p>
<p>Vaccine candidates V590 and V591 (Merck) ^[21]</p>	<p>Vaccine V591 to be based on a modified measles virus that delivers portions of SARS-CoV-2 virus. phase 1 trial ongoing.</p> <p>Vaccine V590 uses Merck's Ebola vaccine technology; human trials ongoing.</p>
<p>COVID-19 S-Trimer (GlaxoSmithKline [GSK]) ^[22]</p>	<p>Partnering with multiple companies using GSK's adjuvants (compounds that enhance vaccine efficacy).</p>
<p>CpG 1018 adjuvant vaccine (Dynavax) ^[23]</p>	<p>Under development with Sanofi's S-protein COVID-19 antigen and GSK's adjuvant technology that stimulates the immune system; phase 1/2 trial ongoing.</p>
<p>UB-612 multipeptide-based vaccine (COVAXX [division of United Biomedical, Inc]) ^[24]</p>	<p>Comprises SARS-CoV-2 amino acid sequences of the receptor binding domain; further formulated with designer Th and CTL epitope peptides derived from the S2 subunit, membrane, and nucleoprotein regions of SARS-CoV-2 structural proteins for induction of memory recall, T-cell activation, and effector functions against SARS-CoV-2.</p>

Vaccine	Comments
	Company partnering with University of Nebraska Medical Center in the United States; phase 1, open-label, dose escalation study ongoing in Taiwan.
HaloVax (Hoth Therapeutics; Voltron Therapeutics) [25]	Collaboration with the Vaccine and Immunotherapy Center at Massachusetts General Hospital; use of VaxCelerate self-assembling vaccine platform offers 1 fixed immune adjuvant and 1 variable immune target to allow rapid development.
Nanoparticle SARS-CoV-2 vaccine (Ufovax) [26]	Vaccine prototype development utilizing self-assembling protein nanoparticle (1c-SapNP) vaccine platform technology.
PDA0203 (PDS Biotechnology Corp) [27]	Utilizes Versamune T-cell-activating platform for vaccine development.
CoVLP recombinant coronavirus virus-like particles (Medicago and GlaxoSmithKline) [28]	Combines Medicago's recombinant coronavirus virus-like particles (rCoVLP) with GSK's adjuvant system; phase 2/3 trial ongoing.
AS03-adjuvanted SCB-2019 (Clover Pharmaceuticals) [44] Subunit vaccine containing SARS-CoV-2 spike (S) protein	Phase 1 trial results reported in December 2020 showed high level of antibodies. Phase 2/3 trial launching by end of 2020 using GSK adjuvant with goal of 34,000 volunteers.
Covaxin (Bharat Biotech and Ocugen) [45] Whole-virion inactivated vaccine	Developed and manufactured in Bharat Biotech's bio-safety level 3 biocontainment facility. Co-development with Ocugen announced for the US market. Elicited strong IgG responses against spike (S1) protein, receptor-binding domain (RBD) and the nucleocapsid (N) protein of SARS-CoV-2 along with strong cellular responses in Phase 1 and 2 clinical trials (n ~1000).

Vaccine	Comments
	Phase 3 trial is in progress in India that involves 26,000 volunteers.
Recombinant adenovirus type-5-vectored vaccine (Ad5-vectored vaccine; Sinopharm [China]) [29]	Approved in China and Saudi Arabia; preliminary data: 86% efficacy; phase 2 trial: seroconversion of neutralizing antibodies seen in 59% and 47% of those in 2-dose groups; seroconversion of binding antibody seen in 96-97% of participants; Positive specific T-cell responses seen in 88-90% of participants.
CoronaVac (Ad5-vectored vaccine; Sinovac [China]) [47]	Limited use in China. Interim phase 3 efficacy reports vary widely from several trials. A trial in Brazil reports efficacy of 50-90%. However, a Turkish trial reports 91.25% efficacy (n = 7,371; data analysis based on 1322 participants – 752 vaccine and 570 placebo).
rAD26 (frozen) and rAd5 vector-based (lyophilized) formulations (Sputnik V; Moscow Gamaleya Institute) [30]	Phase 1/2 trial complete; approved in Russia; both vaccines safe and well tolerated with mostly mild adverse events and no serious adverse events; all participants produced anti-spike protein and neutralizing antibodies after second dose, and generated CD4+ and CD8+ responses.
hAd5 -COVID-19 (ImmunityBio) [31]	Phase 1 trial ongoing; vaccine targets inner nucleocapsid (N) and outer spike (S) protein, which have been engineered to activate T cells and antibodies against SARS-CoV-2, respectively. These dual constructs offer the possibility for the vaccine candidate to provide durable, long-term cell-mediated immunity with potent antibody stimulation to patients against both the S and N proteins.
MRT5500 (Sanofi and Translate Bio) [32]	mRNA-based vaccine candidate; preclinical evaluation demonstrated favorable ability to elicit neutralizing antibodies using a 2-dose schedule administered 3 wk apart; phase 1/2 trial anticipated to start in Q4 2020.
AG0302-COVID19 (AnGes and Brickell Biotech) [33]	Adjuvanted DNA vaccine in phase 1/2 study in Japan; data readouts expected in Q1 2021; intent to follow with phase 3 trials in United States and South America.

Non-Injectable Vaccines in Development

Noninjectable Vaccine	Comments
Intranasal COVID-19 vaccine (AdCOVID; Altimmune, Inc) [34]	Single-dose vaccine; preclinical results completed at University of Alabama Birmingham showed stimulation of antigen-specific CD4+ and CD8+ T-cells in mildly affected lungs as early as 10 d; phase 1 safety and immunogenicity study expected to begin in Q4 2020.
ChAdOx1 nCov-19 inhaled (University of Oxford) [35]	Dose-ranging trial for orally inhaled vaccine beginning phase 1 trials in 30 volunteers in Fall 2020.
saRNA inhaled (Imperial College of London) [35]	Dose-ranging trial for orally inhaled vaccine beginning phase 1 trials in 30 volunteers in Fall 2020.
VXA-CoV2-1 oral vaccine (Vaxart) [36]	Recombinant adenovirus vector type 5 (Ad5) expressing coronavirus antigen and a toll-like receptor 3 (TLR3) agonist as an adjuvant; theorized to confer superior protection compared with injection owing to activation of mucosal immunity; room temperature-stable vaccine tablet entering phase 1 trial in September 2020.
PittCoVacc (University of Pittsburgh School of Medicine) [37]	Vaccine candidate using transdermal microneedle for COVID-19; testing in mice produced antibodies over a 2-wk period; microneedles are made of sugar, making it easy to mass-produce and store without refrigeration.