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The COVID-19 Vaccine Race

A COVID-19 vaccine is a biotechnology product intended to provide acquired immunity against coronavirus disease (COVID-19). Vaccines by definition are biological agents that elicit an immune response to a specific antigen derived from an infectious disease-causing pathogen. As of September 2020, there were 321 vaccine candidates in development, a 2.5-fold increase since April. However, no candidates have completed clinical trials to prove its safety and efficacy. In September, some 39 vaccine candidates were in clinical research, 33 in Phase I–II trials, and 6 in Phase II–III trials, 142 in preclinical evaluation.

Most of the platforms of vaccine candidates in clinical trials as of September2020 are focused on the coronavirus spike protein and its variants as the primary antigen of COVID-19 infection. DNA or messenger RNA, i.e. DNA vaccines or RNA vaccines, offer considerable promise to alter COVID-19 antigen functions for strong immune responses, and can be rapidly assessed, refined for long-term stability, and prepared for large-scale production capacity. Other platforms being developed in 2020 focus on non-replicating viral vectors, peptides, recombinant proteins, live attenuated viruses, and inactivated viruses.

Many vaccine technologies being developed for COVID-19 are not like vaccines already in use to prevent influenza, but rather are using "next-generation" strategies for precision on the COVID-19 infection mechanisms, while hastening development for eventually preventing infection with a new vaccine. Vaccine platforms in development are also designed to address mechanisms for infection susceptibility to COVID-19 in specific population subgroups, such as the elderly, children, pregnant women, and people with existing weakened immune systems.

Types of Vaccine Candidates against COVID-19:

Vaccine type	Mechanism features	Development and production features
Live-attenuated vaccines	Elicit strong immune response, the protection is long lasting, causes reactogenicity	Product development and manufacturing process is highly established but requires handling live virus.
Inactivated vaccines	Less reactogenicity, also weaker immune response than live-attenuated vaccines, requiring multiple dosages and adjuvants	Product development and manufacturing process is highly established but requires handling live virus.

Recombinant protein based and vector based vaccines	Safe, induce a precise immune response, weak immunogenicity, and may require the addition of adjuvants	Epitope selection, antigen design, and vehicle development are not straightforward. Some new-generation vaccine types were not produced on large scale before.
Trained immunity based vaccine	May boost the innate immunity against a wide range of infectious agent, the efficacy, and mechanisms are still under study	Current available across the world, but each country has its version. Not the traditional specifific adaptive immunity inducing vaccine.

Preclinical Testing:

In a Preclinical trial, the vaccine is given to animals such as mice or monkeys, typically rhesus macaques (Macaca mulatta), to see if it produces an immune response

Phase 1:

In a Phase I trial, the vaccine candidate is given to a small number of people to test safety and dosage as well as to confirm that it stimulates the immune system.

Phase 2:

In a Phase II trial, the vaccine candidate is given to hundreds of people split into different age or risk groups to see if the vaccine acts differently in different populations. These trials further test the vaccine's safety and ability to stimulate the immune system.

Phase 3:

In a Phase III trial, the vaccine candidate is given to thousands of people and wait to see how many become infected, compared with those who received a placebo. These trials can determine if the vaccine protects against the coronavirus.

Approval:

Regulators in each country review the trial results and decide whether to approve the vaccine or not. During a public health emergency, a vaccine may receive Emergency Use Authorization (EUA) before getting formal approval.

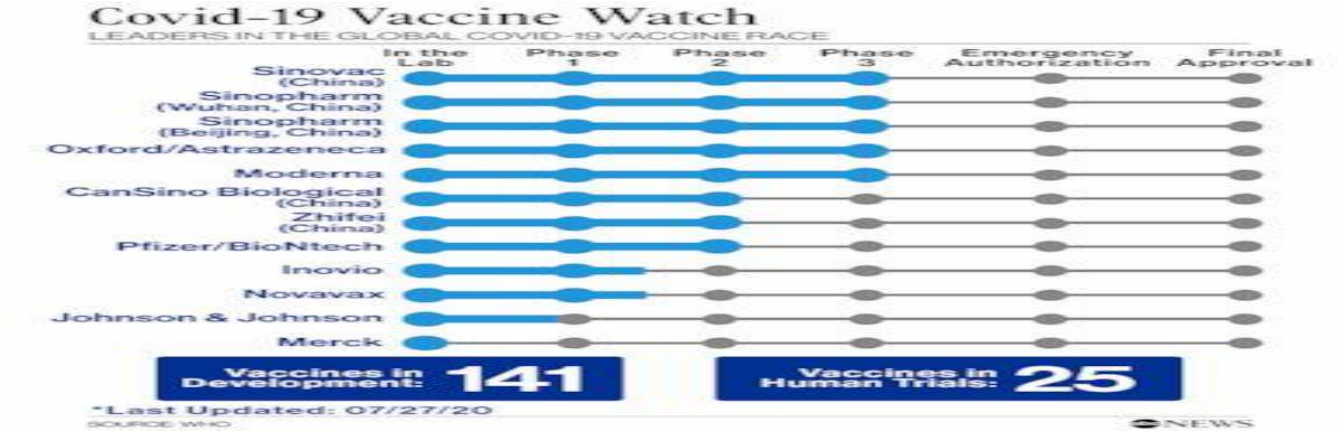
Phase 4:

In a Phase IV trial – also known as a post marketing surveillance trial or a confirmatory trial – the vaccine is monitored for safety, side effects and efficacy after it has been approved and made available to the public.

Combined Phases:

Some coronavirus vaccines are now in combined phase trials to speed evaluation. For instance, many Phase 1/2 trials are underway to test a vaccine for the first time on hundreds of people.

COVID−19: candidate vaccines in Phase I–III trials:



Vaccine candidates Developers, Sponsors	Technology	Current phase (participants) Design	Completed phase (participants) Immune response, adverse effects	Duration
AZD1222 University of Oxford, AstraZeneca	Modified chimp adenovirus vector (ChAdOx1)	Phase III (30,000) Interventional; randomized, placebo-controlled study for efficacy, safety, and immunogenicity. Brazil (5,000) International enrollment of the Phase III trial was paused on 8 September 2020 due to an adverse neurological event in one participant, but resumed on 12 September after it was determined the symptoms were unrelated to the vaccine.	Phase I-II (543) Spike-specific antibodies at day 28; neutralizing antibodies after a booster dose at day 56. Adverse effects: Pain at the injection site, headache, fever, chills, muscle ache, malaise in more than 60% of participants; paracetamol allowed for some participants to increase tolerability.	May 2020 - Aug 2021

Unnamed Sinopharm: Beijing Institute of Biological Products, Wuhan Institute of Biological Products	Inactivated SARS-CoV-2 (vero cells)	Phase III (45,000) Randomized, double-blind, parallel placebo-controlled, to evaluate safety and protective efficacy in the United Arab Emirates, Bahrain, and Jordan. On September 14, UAE approved Sinopharm's vaccine for emergency use by front-line healthcare workers following successful interim results in the Phase III trials.	Phase I-II (320) Neutralizing antibodies at day 14 after 2 injections; Adverse effects: injection site pain and fever, which were mild and self-limiting; no serious effects.	Jul 2020- Jul 2021 in Abu Dhabi
Ad5-nCoV CanSinoBIO, Beijing Institute of Biotechnology of the Academy of Military Medical Sciences	Recombinant adenovirus type 5 vector	Phase III (40,000) global multi-center, randomized, double-blind, placebo -controlled to evaluate efficacy, safety and immunogenicity	Phase II (508) Neutralizing antibody and T cell responses. Adverse effects: moderate over 7 days: 74% had fever, pain, fatigue	Mar - Dec 2020 in China Sep 2020 - Dec 2021 in Pakistan
CoronaVac Sinovac, Instituto Butantan	Inactivated SARS-CoV-2	Phase III (10,490) Double-blind, randomized, placebo-controlled to evaluate efficacy and safety in Brazil (8,870); Indonesia (1,620)	Phase II (600) Preprint. Immunogenicity eliciting 92% seroconversion at lower dose; Adverse effects: mild in severity, pain at injection. Site.	Jul 2020 - Oct 2021 in Brazil Aug 2020 - Jan 2021 in Bandung, Indonesia

BNT162 a1, b1, b2, c2 BioNTech, Fosun Pharma, Pfizer	mRNA	Phase III (30,000) Randomized, placebo-controlled	Phase I-II (60) Preprint. Strong RBD-binding IgG and neutralizing antibody response peaked 7 days after a booster dose, robust CD4+ and CD8+ T cell responses, undetermined durability. Adverse effects: dose-dependent and moderate including pain at the injection site, fatigue, headache, chills, muscle and join pain, fever	Apr 2020 - May 2021
mRNA-1273 Moderna, NIAID, BARDA	Lipid nanoparticle dispersion containing mRNA	Phase III (30,000) Interventional; randomized, placebo-controlled study for efficacy, safety, and immunogenicity	Phase I (45) Dose-dependent neutralizing antibody response on two-dose schedule; undetermined durability. Adverse effects: fever, fatigue, headache, muscle ache, and pain at the injection Site.	Jul 2020 - Oct 2022

Vaccine candidates:

CEPI (CEPI Coalition for Epidemic Preparedness Innovations is a new alliance between governments, industry, academia, philanthropy, intergovernmental institutions, such as the World Health Organization, and civil society classifies development stages for vaccines as:

1- "exploratory" (planning and designing a candidate, having no evaluation in vivo),

2- "preclinical" (in vivo evaluation with preparation for manufacturing a compound to test in humans), or initiation of Phase I safety studies in healthy people.

Some 321 total vaccine candidates are in development as either confirmed projects in clinical trials or in early-stage "exploratory" or "preclinical" development, as of September.

Phase I trials test primarily for safety and preliminary dosing in a few dozen healthy subjects, while Phase II trials – following success in Phase I – evaluate immunogenicity, dose levels (efficacy based on biomarkers) and adverse effects of the candidate vaccine, typically in hundreds of people. A Phase I–II trial consists of preliminary safety and immunogenicity testing, is typically randomized, placebo-controlled, and at multiple sites, while determining more precise, effective doses. Phase III trials typically involve more participants, including a control group, and test effectiveness of the vaccine to prevent the disease (an "interventional" trial), while monitoring for adverse effects at the optimal dose. Definition of vaccine safety, efficacy, and clinical endpoints in a Phase III trial may vary between the trials of different companies, such as defining the degree of side effects, infection or amount of transmission, and whether the vaccine prevents moderate or severe COVID-19 infection.

BCG & MMR Trails:-

Assertions have been made that COVID-19 mortality has been lower in countries having routine BCG vaccine administered against tuberculosis though the World Health Organization (WHO) has said there is no evidence that this vaccine is effective against the COVID-19 virus.

In March 2020, a randomized trial of BCG vaccine to reduce COVID-19 illness began in the Netherlands, seeking to recruit 1,000 healthcare workers. A further randomized trial in Australia is seeking to enroll 4,170 healthcare workers. A further 700 healthcare workers from Boston and Houston will be recruited in another trial, and 900 healthcare workers in Egypt are to participate in a trial registered by a university in Cairo, Egypt. An additional trial in the Netherlands is testing whether BCG vaccine provides protection for older people, recruiting 1,000 people over 65 years and 600 younger adults. A trial of BCG in 1,000 healthcare workers in Medellín, Colombia was registered on 24 April 2020. Other trials of BCG in healthcare workers were registered in late April – early May: 1,100 participants in Brazil, 1,120 in France, 1,500 in Denmark, and 500 in South Africa. In May 2020, a trial seeking 900 people over 50 in Greece to test BCG vaccine as protection against COVID-19 was registered.

In June 2020, a randomized placebo-controlled trial to test whether the measles-mumps-rubella vaccine (MMR) can protect healthcare workers from COVID-19 began with 200 participants in Cairo.

Use of adjuvants:

In September 2020, eleven of the vaccine candidates in clinical development used adjuvants to enhance immunogenicity. An immunological adjuvant is a substance formulated with a vaccine to elevate the immune response to an antigen, such as the COVID-19 virus or influenza virus. Specifically, an adjuvant may be used in formulating a COVID-19 vaccine candidate to boost its immunogenicity and efficacy to reduce or prevent COVID-19 infection in vaccinated individuals. Adjuvants used in COVID-19 vaccine formulation may be particularly effective for technologies using the inactivated COVID-19 virus and recombinant protein-based or vector-based vaccines. Aluminum salts, known as "alum", were the first adjuvant used for licensed vaccines, and are the adjuvant of choice in some 80% of adjuvant vaccines. The alum adjuvant initiates diverse molecular and cellular mechanisms to enhance immunogenicity, including release of proinflammatory cytokines. A potential drawback of adjuvant vaccines is that the virus evolves in a way to avoid the induced vaccine response, making the adjuvant-vaccine technology misdesigned against a changed virus. Such a change would require revised manufacturing and increased costs that discourage the routine use of adjuvants.

Antibody-dependent enhancement:

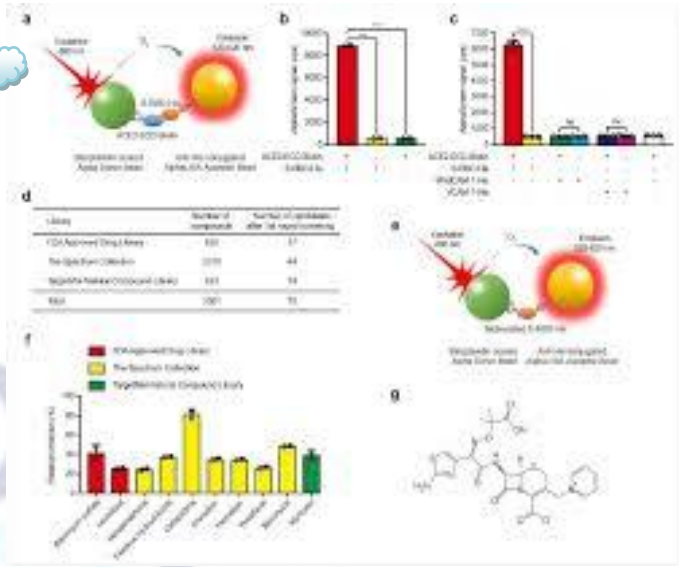
Although the quality and quantity of antibody production by a potential vaccine is intended to neutralize the COVID-19 infection, a vaccine may have an unintended opposite effect by causing antibody-dependent disease enhancement (ADE), which increases the virus attachment to its target cells and might trigger the cytokine storm when the person will be infected by the virus after vaccination. The vaccine technology platform (for example, viral vector vaccine, spike (S) protein vaccine or protein subunit vaccine), vaccine dose, timing of repeat vaccinations for the possible recurrence of COVID-19 infection, and elderly age are factors determining the risk and extent of ADE. The antibody response to a vaccine is a variable of vaccine technologies in development, including whether the vaccine has precision in its mechanism and choice of the route for how it is given (intramuscular, intradermal, oral, or nasal).

Efficacy:

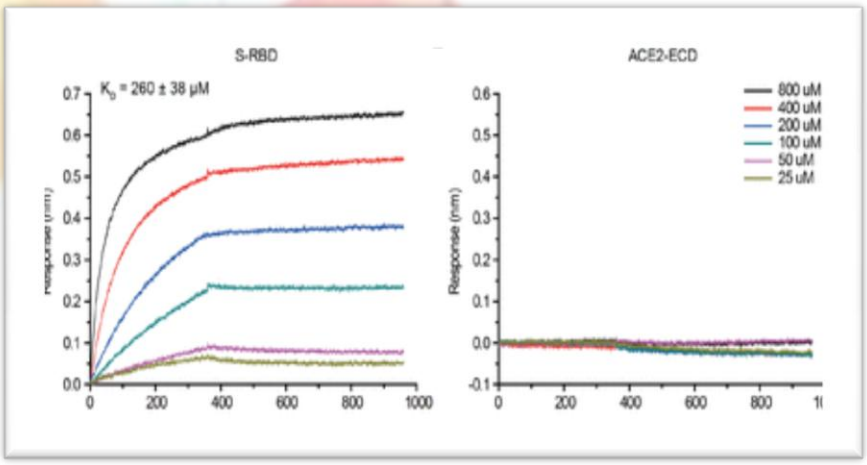
The effectiveness of new vaccine is defined by its efficacy. The efficacy of less than 60% may result in failure to create herd immunity. Host-("vaccinee")-related determinants that render a person susceptible to infection, such as genetics, health status (underlying disease, nutrition, pregnancy, sensitivities or allergies), immune competence, age, and economic impact or cultural environment can be primary or secondary factors affecting the severity of infection and response to a vaccine. Elderly (above age 60), allergen-hypersensitive, and obese people have susceptibility to compromised immunogenicity, which prevents or inhibits vaccine effectiveness, possibly requiring separate vaccine technologies for these specific populations or repetitive booster vaccinations to limit virus transmission. Further, mutations of the virus can alter its structure targeted by the vaccine, thus making the vaccine ineffective.

Ceftazidime as Anti-viral !

Ceftazidime is a potential drug to inhibit SARS-CoV-2 infection in vitro by Blocking Spike Protein-ACE2 Interaction .Cell entry of SARS-CoV-2 mainly depends on binding of the viral spike (S) proteins to angiotensin converting enzyme 2 (ACE2) on host cells. Therefore, repurposing of known drugs to inhibit S protein-ACE2 interaction could be a quick way to develop effective therapy for COVID-19. Using a high-throughput screening system to investigate the interaction between spike receptor binding domain (S-RBD) and ACE2 extracellular domain, They screened 3581 FDA-approved drugs and natural small molecules and identified ceftazidime as a potent compound to inhibit S-RBD–ACE2 interaction by binding to S-RBD.



In addition to significantly inhibit S-RBD binding to HPAEpiC cells,
Ceftazidime efficiently prevented SARS-CoV-2 pseudovirus to infect ACE2-expressing 293T cells.
The inhibitory concentration (IC50) was 113.2 µM, which is far below the blood concentration (over 300 µM) of ceftazidime in patients when clinicallytreated with recommended dose. Notably, Ceftazidime is a drug clinically used for the treatment of pneumonia with minimal side effects compared with other antiviral drugs. Thus, ceftazidime has both anti-bacterial and anti-SARS-CoV-2 effects ,which should be the first-line antibiotics used for the clinical treatment of COVID-19.



Ex. BinBinding profiles of ceftazidime to S-RBD and ACE2-ECD were measured by bio-layer interferometry in an Octet RED96 instrument

There is no time to waste in the fight against COVID-19

No-one is safe until everyone is safe.

References:

1. "Draft landscape of COVID 19 candidate vaccines". World Health Organization. 17 September 2020. Retrieved 17 September 2020.
2. https://clinicaltrials.gov/ct2/results?term=covid+vaccine&draw=2&rank=2#rowId1
3. Funk CD, Laferrière C, Ardakani A (2020). "A Snapshot of the Global Race for Vaccines Targeting SARS-CoV-2 and the COVID-19 Pandemic". Front Pharmacol. 11: 937. doi:10.3389/fphar.2020.00937. PMC 7317023. PMID 32636754.
4. "Safety and Immunogenicity Study of an Inactivated SARS-CoV-2 Vaccine for Preventing Against COVID-19". ClinicalTrials.gov (Registry). United States National Library of Medicine. 2 June 2020.. Retrieved 14 July 2020.
5. Le, Tung Thanh; Cramer, Jakob P.; Chen, Robert; Mayhew, Stephen (4 September 2020). "Evolution of the COVID-19 vaccine development landscape". Nature Reviews Drug Discovery.
6. https://relief.unboundmedicine.com/relief/view/Coronavirus-Guidelines/2355056/all/Coronavirus_COVID_19_Vaccines
7. https://www.sciencedirect.com/science/article/pii/S2590098620300361
8. https://cepi.net/COVAX/
9. https://www.gavi.org/vaccineswork/covid-19-vaccine-race
10. https://www.biorxiv.org/content/10.1101/2020.09.14.295956v1.full