Overview of SARS-CoV-2 and COVID-19 Vaccine

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The COVID-19 pandemic has devastating effects the world over imprudently. Developing a safe and effective vaccine is the key to fight the disease. This review aims to epitomize the vaccines development processes, suitable and potential vaccine candidates and their trail studies. The vaccine development started earlier in January 2020 after the genomic sequence of coronavirus was revealed. The most pronounced and successful vaccine candidates, trials of which have been conducted worldwide include BNT-162b2 (Pfizer, BioNTech), mRNA-1273 (Moderna), NVX-CoV2373 (Novavax), and AZA-1222 Ad-5-CoV (AstraZeneca). Many other injectable and noninjectable vaccines are under trails, and the struggle for most suitable vaccine for market launch is going on. The foremost challenges related to vaccine development are its logistic and storage complications, and scientists are working tirelessly to overcome these challenges.

Key words: COVID-19, SARS-CoV-2, Vaccine, Efficacy, Safety

INTRODUCTION

The pandemic of SARS-CoV-2, novel coronavirus is a respiratory contagion that emanated from China in late 2019 and outspread globally effecting millions of people. The disease is airborne and characterized by a variety of clinical manifestations ranging from asymptomatic course of disease to flu like symptoms, and in severe cases mechanical ventilation is necessitated[1]. Evidence suggest that immunity plays vital role in ascertaining disease severity and also help combating the viral infection. Research has indicated diverging molecular phenotypes that might result in diverse outcomes of disease in different regions of the world[2]. Initially, the COVID-19 induced lung damage and inflammatory cytokines flounce was the major attribute of the pathophysiology of the disease. However, research-based evidence later elaborated the phenomenon after the viral genome was revealed. Epidemiological studies alarmed higher risk in elderly and patients with co-morbidities, especially cardiovascular disorders and diabetes[3]. The disease management ranges from home quarantine in uncomplicated disease and early recovery to hospitalization in intensive care unit and need for mechanical ventilation in complex severe acute respiratory distress. Classical public health precautions such as isolation, hygiene practice, and social distancing are the best preventive measures, also important for self-limiting uncomplicated disease. No evidence of specific drug-therapy has been identified for the treatment of either mild or severe SARS-CoV-2 infection[4]. Apart from the symptomatic treatment and management, certain antiviral drugs; Lopinavir, Umifenovir, Remdesivir have undergone clinical trials ever since the COVID-19 has existed[5]. Use of convalescent plasma has also been considered potential treatment option in coronavirus disease. The challenge posed by the disease are management of respiratory complications and immunization.

CORONAVIRUS VACCINE DEVELOPMENT

There is a striking resemblance between SARS-CoV and the novel SARS-CoV-2, but the rapid spread and more devastating effects of novel coronavirus are attributed to its genomic evolution. The coronavirus is a positive sense single strand of RNA. The envelope has glycoproteins projections derived from the host and the whole viral entity appears spherically[6]. Among the five structural proteins encoded by genome of novel coronavirus, namely spike (S), membrane (M), envelope (E), nucleocapsid (N), hemagglutinin-esterase (HE), the virus gets attached to host cell surface through spikes (S)[7] and interacts with Angiotensin converting enzyme-2 (ACE-2) receptor[8]. The virus replicates through messenger RNA (mRNA). The replication phenomenon leads to the alpha, beta, gamma and delta subtypes among which beta-coronavirus is believed to the current COVID-19 pandemic[9].

Vaccination and immunization are believed to be effective in immune strengthening and disease prevention. After the genetic sequence of coronavirus was revealed in January 2020, ample research has been carried out to find the best suitable candidate for the vaccine development. By the start of January 2021, 66 vaccines have been entered into clinical trials, of which 20 have entered in final phase of testing, and 90 are still in preclinical animal studies[10].

Table 1: Coronavirus Vaccine Candidates

Trial Phase/ Approval	Studies	No. of Vaccines
I	Safety and dosage testing	38
II	Expanded safety trails	24
III	Large scale efficacy	20
Limited	Vaccines in early use or approved for limited use	8
Approved	Approved for full use	2
Abandoned	Deserted after clinical trials	3

Vaccine development is a complex process, and it is arduous to find the best efficacious candidate among a pool of vaccine candidates. Technology considerations in the development of coronavirus vaccine include molecular approach such as DNA, RNA, and protein subunit, attenuated and viral vector. Depending upon the type of technology employed, attributes of vaccines differ in terms of dosage, storage and scalability of production. Some of the technologies such as mRNA have already been cast-off for influenza, Zika virus, and rabies and tested in animals as well. Nucleic acid-based vaccine candidates have proven to be safer and efficacious in early trials and are projected for expanded trials in large population. Many countries including United States, Europe, and the United Kingdome have lunched official trails of the vaccine candidates.

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Table 2: Vaccine Candidates with Worldwide Trials

Technology	Characteristics	Doses	Candidate Vaccine	Manufacturer
mRNA	Detonate developing speed, medium-low production scale	2	BNT-162b2	Pfizer, BioNTech
			mRNA-1273	Moderna
DNA	Fast development speed, medium production scale	2	INO-4800	Inovio
Protein subunit	Medium to fast development, high production scale	2	NVX-CoV2373	Novavax
Viral Vector	Medium developing, higher production	1-2	AZA-1222 Ad-5-CoV	AstraZeneca
			Ad26. COV2.S	Johnson & Johnson

By the end December 2020, many vaccine candidates successfully gained authorization for emergency use in various countries. These vaccines are in last stage development or have completed phase-III clinical trials. Despite the fact that vaccine is equally important for immunity against COVID-19 in all people, vaccines approved for full use are presumed to be initially injected to high-risk groups, i.e., healthcare workers, elderly, and comorbid individuals[11]. The vaccination planner has also consideration of gaining public confidence by injecting vaccine to healthcare workers and government officials.

Ad5-nCoV immunization up-and-comer, created by CanSino Biologics in China, has as of late demonstrated accomplishment with their two vaccines dosages going through Phase-III safety trials. The two experimental groups of inoculated members create counter-acting agent reactions in 47–59% of the volunteers and seroconversion of binding antibodies in 96–97% of them[13].

Another promising vaccine, the ChAdOx1 nCoV19 (AZD1222) adenovirus vector immunization created by the University of Oxford in the United Kingdom, was tried for wellbeing and viability. They utilized the meningococcal form antibody as a control and the homologous boosting meetings indicated increments in humoral and cell resistant reactions in individuals tested. The most noticeable adverse effect was soreness at injection site[14].

The American Biotechnology organization, Moderna, Inc. is in cycle of building up the mRNA-1273 immunization. This vaccine is made with powerful lipid nanoparticle scattering containing mRNA encoding for the SARS-CoV-2 spike protein. The quick assembling of this immunization made it to the first-in-human clinical preliminaries. In addition, immunization advancement timetables were dense to two to a half year in the wake of accepting their Fast-Track Designation mid-May 2020. The stage II preliminary of the mRNA-1273 immunization helped in effectively distinguish high killing immunizer reactions which expanded in a portion subordinate way. Nonetheless, the Gam-COVID-Vac-Lyo being created in Russia has finished the assortment of essential result recorded by August 2020. In any case, Russian specialists have chosen to give this immunization a crisis use approval regardless of the way that stage III clinical preliminaries have not been finished.

PROMINENT VACCINES OVERVIEW

1. BNT-162b2

- Genetic encoded vaccine
- Capacity and delivery necessities: Frozen; super cool stockpiling of - 70ºC

Table 3: COVID-19 Vaccines in Clinical Trials Progression[9,12]

Technology	Vaccine Candidate	Country of trial study	Trial Phase
Classical Remodeled Vaccines	Bacillus Calmette-Guerin (BCG)	Australia	III
	CoronaVac (PicoVac)	China	III
Attenuated Virus Vaccine	Unspecified	China	I, II
	Unspecified (Pneumonia vaccine)		III
	CDX-005 (CDX-CoV)	UAE	III
	Ad5-nCoV	United Kingdom	III
	ChAdOx1 nCoV19 and COVID-19/aAPC	China	I, II
Viral Vector Vaccine	Gam-COVID-Vac Lyo	Russia	III
	Ad26.COV2-S	United States	III
	Ad26.COV2-S		Preclinical
	rVSVΔG-SARS-CoV-2		Preclinical
RNA Based Vaccine	mRNA-1273	Germany, United States	III
	BNT162	United Kingdom	I
	LNP-nCoVsaRNA	Germany	II
DNA Based Vaccine	ARCoV	Korea	I
	INO-4800		I, II
	GX-19	Australia	I/II
Protein Vaccine	NVX-CoV2373	Australia	I
	SCB-2019	United States	II
	Oral recombinant VAAST	China	I
	Adjuvant recombinant protein	United States	I
Genetically Engineered Bacterial Vaccine	CoV RBD219-N1	Canada	I

- Requires reconstitution
- When defrosted, stable while refrigerated for as long as 5 days
- Room temperature solidness: 2 hours
- Dosage: two intramuscular injections in deltoid muscle separated by 21 days.

BNT-152b2 launched by Pfizer is a nucleoside-adjusted mRNA (modRNA) immunization serum that encodes an improved SARS-CoV-2 receptor-binding domain (RBD) antigen. The continuous global phase 3 preliminary testing included 43,548 members 16 years and above allocated randomly to get injected with vaccine and placebo; 43,448 members got immunization or placebo treatment (vaccinated group: 21,720, and placebo group: 21,728). The phase-3 trials of BNT-162b2 included about 42% of worldwide individuals and 30% of US entrants were of racially and ethnically different foundations, and 41% of worldwide and 45% of US members were 56-85 years old. Efficacy of vaccine was found to be 95%, and no genuine safety issues were noticed. Among the serious adverse effects were the recurrence weakness at 3.8%; while headache happened in 2% of individuals. Transient muscle soreness and pain at injection site was the most normally revealed response, and serious agony happened in under 1% of members across all age groups.

2. mRNA-1273

- Genetically encoded vaccine
- Dosage: 2 infusions separated by 28 days
- Infused undiluted
- Supply chain and long-haul stockpiling: Frozen (- 20°C) for a half year
- Subsequent to defrosting: Standard refrigeration temperatures (2-8°C) for 30 days
- Room temperature: Up to 12 hours

The mRNA-1273 vaccine developed by Moderna encodes the S-2P antigen. The phase-III trails in United States (COVE) dispatched on July 27, 2020. The preliminary study was led in participation with the National Institute of Allergy and Infectious Diseases and included in excess of 30,000 members who got 2 100-µg portions or coordinated placebo on days 1 and 29. The first efficacy study report was delivered November 30, 2020. The COVE study (n = 30,420) included United States individuals of age 65 years and above (24.8%), young population with high susceptibility for COVID-19 (16.7%), people who were recognized as Hispanic or Latin (20.5%), and people who distinguish as Black or African American (10.4%)[15].

Immunogenicity information at 90 days after the subsequent vaccination was assessed in 34 members in the phase 3 clinical trials. A stage 2/3 preliminary study in teenagers 12-17 years started in December 2020 is required to select 3,000 members[16].

3. AZD-1222

- Viral vector vaccine
- Phase-III trial was incidentally required to be postponed worldwide on September 6, 2020 after an investigation member in the United Kingdom was determined to have cross over myelitis. After FDA audit in the United States, trials recommenced on October 23, 2020.
- Storage: Refrigeration
- Dosage: 2 injections separated by 28 days

AZD-1222 (ChAdOx1 nCoV-19; AstraZeneca) is a replication-lacking chimpanzee adenoviral vector vaccine containing the surface glycoprotein antigen (spike protein) gene. This vaccine takes action framework by evoking antibodies to assault the SARS-CoV-2 infection in the event that it later invades the body. Attributable to the testing of an alternate Covid antibody lately, developmental progress for AZD-1222 was quicker than that of other viral vector vaccines. Outcomes of investigation of the phase 3 clinical preliminary in the United Kingdom, Brazil, and South Africa are as per the following:

Single dose (n = 2741) indicated efficacy of 90% when given as a half dose, trailed by a full dose one month after the first. Another dosage schedule (n = 8895) demonstrated 62% efficacy when administered as 2 full dosage with gap of 30 days. The consolidated evaluation from both dosing regimens (N = 11,636) brought about an efficacy of 70.4%. All outcomes were statistically remarkable ($p< .0001$)[17]. The phase 3 efficacy studies in the United States are progressing.

4. Ad26.COV2. S

- Viral vector antibody
- Transportation and long-term storage: Frozen (- 20ºC) for as long as 2 years
- Post defrosting: Standard fridge temperatures (2-8ºC) for as long as 3 months
- Portion: 1 infusion

The stage 3 trials (ENSEMBLE) for adenovirus serotype 26 (Ad26) recombinant vector-based vaccine (JNJ-78436735; Johnson and Johnson) was dispatched in September 2020 in the United States, South Africa, and South America. In December 2020, the trial was completely enlisted with around 45,000 members. Interval results for the phase 1/2a trial depicting killing immune response titers of over 90% at day 29 and 100% at day 57 were distributed in January 2021[18].

The vaccination utilizes Janssen's AdVac innovation, which upgrades physicochemical and biological stability of vaccine (i.e., 2 years at -20ºC and at any rate 3 months at 2-8ºC). This makes the candidate vaccine comparable with standard distribution channels and new logistic structure would not be needed for conveyance to individuals who need it. A second phase 3 trial (EMSEMBLE 2) to notice impacts of 2 dosages of the vaccine in up to 30,000 members overall was reported on November 15, 2020[19].

5. NVX-CoV2373

- Protein subunit vaccine
- Dose: 2 infusions, 21 days apart

NVX-CoV2373 (Novavax) is developed utilizing recombinant nanoparticle innovation from genetic sequence of SARS-CoV-2 to produce an antigen got from the viral spike protein. This is joined with an adjuvant (Matrix-M). Aftereffects of preclinical examinations indicated that it binds successfully and more effectively with human receptors targeted by the virus. Phase 1/2 preliminary studies were started in May 2020. Phase 1 information in sound grown-ups indicated that the adjuvanted immunization prompted balance titers that surpassed reactions in recuperating serum from patients with COVID-19[20].

The phase 3 trial in the United Kingdom has finished enlistment of 15,000 members, including over 25% individuals of age greater than 65 years. Analysts leading the United State and Mexico phase 3 trial, which began in December 2020, plan to enlist up to 30,000 members.

PHARMACEUTICALLY MODIFIED- NON-INJECTABLE VACCINES

Researchers and pharmaceutical firms are also working to develop vaccine administered through routes other than injection.

Noninjectable Vaccine	Description	Developer/Study Conductor
Intranasal COVID-19 vaccine (AdCOVID)	• Single-dose vaccine; preclinical outcomes finished at University of Alabama Birmingham indicated incitement of antigen-explicit CD4+ and CD8+ T-cells in somewhat influenced lungs as right on time as 10 d. • Phase 1 safety and immunogenicity study started in Q4 2020[21].	Altimmune Inc.
ChAdOx1 nCov-19 (inhalational vaccine)	• Orally inhaled vaccine trials started in fall 2020[22].	University of Oxford
saRNA inhaled	• Orally inhaled vaccine trials started in fall 2020[22].	Imperial College London
VXA-CoV2-1 oral vaccine	• Recombinant adenovirus vector type 5 (Ad5) communicating COVID antigen and a toll like receptor 3 (TLR3) agonist as an adjuvant; conjectured to meet better efficacy than injectable due to actuation of mucosal immunity. • Room temperature-stable tablet entered phase-1 trials in September 2020[23].	Vaxart
PittCoVacc	• Vaccine contender utilizing transdermal microneedle for COVID-19; testing in mice created antibodies over a 2-wk period. • Microneedles are made of sugar, making it simple to mass-produce and store without refrigeration[24].	University of Pittsburgh

Table 4: Other Investigational Vaccines

Vaccine	Developer (s)	Preliminary Results
CVnCoV	CureVac & Bayer	Fundamental information from phase 1 dose raising trail: 12-µg dose gave IgG neutralizer levels similar to plasma. Continuous stage 2b/3 preliminary enlistment (35,000 volunteers in Europe and Latin America).
Vaccine candidates V590 and V591	Merck	Trial 1 undergone in late 2020 of V591 based on modification of measles virus which delivers portions of SARDS-CoV-2 virus.
COVID-19 S-Trimer	GlaxoSmithKline (GSK)	Banding together with various organizations utilizing GSK's adjuvants (that upgrades vaccine efficacy).
Nanoparticle SARS-CoV-2 vaccine	Ufovax	Vaccine prototype development utilizing self-assembling protein nanoparticle (1c-SapNP) vaccine platform technology.
AS03-adjuvanted SCB-2019 Subunit vaccine containing SARS-CoV-2 spike (S) protein	Clover Pharmaceuticals	Outcomes of Phase-1 trials revealed in December 2020 indicated significant increase in antibodies level. Phase 2 and 3 trials were instigated in the end of December 2020, utilizing GSK adjuvant with recruitment of 34,000 volunteers.
UB-612 multitope peptide-based vaccine	United Biomedical, Inc.	It involves SARS-CoV-2 amino acid of host cell RBD, further enhances structurally with Th and CTL epitope peptides got from the S2 subunit, layer, and nucleoprotein districts of SARS-CoV-2 primary proteins for enlistment of memory recall, T-cell initiation, and effector capacities against SARS-CoV-2.
rAD26 (frozen) and rAd5 vector-based (lyophilized) formulations	Sputnik V; Moscow Gamaleya Institute	Stage 1/2 preliminary complete; affirmed in Russi, Italy; the two vaccines have broader safety profile, and so serious adverse event has been reported; all tested members created hostile to spike protein and killing antibodies after administration of second dose, and produced CD4+ and CD8+ retaliation.

Plenty of vaccine development projects are under investigation at various stages of clinical trials around the world.

CONCLUSION

The COVID-19 pandemic has impacted countries around the globe. Building up a successful, safe and cost-effective vaccine is a significant methodology to battle this pandemic. There are a few vaccine contenders in clinical preliminaries right now with the soonest expected to arrive at the market by the mid of 2021. The exigent need of vaccine and out of the various challenges in its development, researchers and authorities need to expedite their efforts in securing a sufficient lot of vaccine which is stable, safe, and economic. Moderateness in storage conditions for vaccines will allow its transport and accessibility for all.

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REFERENCES

1. Aschenbrenner AC, Mouktaroudi M, Krämer B, et al. Disease severity-specific neutrophil signatures in blood transcriptomes stratify COVID-19 patients. Genome Med 2021;13(1):7.
2. Ong EZ, Chan YFZ, Leong WY, et al. A Dynamic Immune Response Shapes COVID-19 Progression. Cell Host Microbe 2020;27(6):879-82.
3. Sanyaolu A, Okorie C, Marinkovic A, et al. Comorbidity and its Impact on Patients with COVID-19. SN Compr Clin Med 2020;1-8.
4. Zhai P, Ding Y, Wu X, et al. The epidemiology, diagnosis and treatment of COVID-19. Int J Antimicrob Agents 2020;55(5):105955.

5. Hussain N, Yoganathan A, Hewage S, et al. The effect of antivirals on COVID-19: a systematic review. Expert Rev Anti Infect Ther 2020;1-14.
6. Baron S. Medical Microbiology. 4th ed. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. ISBN-10: 0-9631172-1-1.
7. Rabaan AA, Al-Ahmed SH, Haque S, et al. SARS-CoV-2, SARS-CoV, and MERS-COV: A comparative overview. Infez Med 2020;28(2):174-84.
8. Jeyanathan M, Afkhami S, Smaill F, et al. Immunological considerations for COVID-19 vaccine strategies. Nat Rev Immunol 2020;20(10):615-32.
9. Raja AT, Alshamsan A, Al-jedai A. Current COVID-19 vaccine candidates: Implications in the Saudi population. Saudi Pharm J 2020; 28(12):1743-8.
10. Zimmer C, Corum J, Wee SL. Coronavirus Vaccine Tracker, New York: The New York Times. 2021.
11. Smith C. The structural vulnerability of healthcare workers during COVID-19: Observations on the social context of risk and the equitable distribution of resources. Soc Sci Med 2020; 258: 113119.
12. Le TT, Cramer JP, Chen R, et al. Evolution of the COVID-19 vaccine development landscape. Nat Rev Drug Discov 2020;19(10):667-8.
13. Zhu FC, Guan XH, Li YH, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomized, double-blind, placebo-controlled, phase 2 trial. Lancet 2020;396(10249):479-88.
14. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med 2020;383(20):1920-31.
15. Baden LR, El Sahly HM, El Sahly B, et al., Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. New Engl J Med 2021; 384:403-16.
16. Widge AT, Rouphael NG, Jackson LA, et al. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. N Engl J Med 2021;384(1):80-2.
17. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomized controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397(10269):99-111.
18. Sadoff J, Le Gars M, Shukarev G, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2. S Covid-19 Vaccine. N Engl J Med 2021; NEJMoa2034201.
19. U.S. National Library of Medicine. A Study of Ad26.COV2. S for the Prevention of SARS-CoV-2-Mediated COVID-19 in Adult Participants (ENSEMBLE). 2021.
20. Keech C, Albert G, Cho I, et al., Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. New Engl J Med 2020; 383(24): 2320-32.
21. U.S. National Library of Medicine. NasoVAX in Patients with Early Coronavirus Infectious Disease 2019 (COVID-19). 2020.
22. O'Hare R. Landmark coronavirus study to trial inhaled Imperial and Oxford vaccines, London: Imperial College London, 2020.
23. VAXART. Vaxart Announces FDA Clearance of IND Application for Oral COVID-19 Vaccine and Provides Update on COVID-19 Program. South San Francisco, Calif., Sept. 14, 2020 (GLOBE NEWSWIRE) -Vaxart, Inc.
24. Kim E, Erdos G, Huang S, et al. Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development. EBioMedicine 2020; 55:102743.