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Review

Current COVID-19 vaccine candidates: Implications in the Saudi population

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ABSTRACT

Aim: The purpose of this review is to discuss the current status of local and international efforts undergoing clinical trials aiming at developing a Coronavirus Disease-2019 (COVID-19) vaccine, and to highlight the anticipated challenges of this vaccine globally and in Saudi Arabia.

Present Findings: COVID-19 vaccine development efforts started in early January 2020 when Chinese scientists shared the Coronavirus genomic sequence in public domain. Approximately 321 research groups initiated the search for a vaccine, out of which 41 have reached phase I/II trails and 11 reached phase-III clinical trials, including approved vaccines for early to limited use. Out of these projects are two labs in the Kingdom of Saudi Arabia still in early stages of development of a COVID-19 vaccine. Several vaccine attempts are being tested from traditional, attenuated virus methods, to new nucleic acid-based designs. However, no vaccine has yet completed clinical trials and reached public domain.

In spite of the challenges faced during previous vaccine trials, researchers have found that Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the causative agent of COVID-19 is structurally similar to the (SARS-CoV-1) and the Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV), which caused epidemics in 2003 and 2012 respectively. Both SARS strains show identical affinity towards the type-II alveolar pneumocytes angiotensin converting enzyme-2 (ACE-2) receptor binding domains and therefore, similar pathogenicity. The race to develop the vaccine is predominantly for individuals at high risk of developing the infection, i.e. population groups who are most susceptible to experiencing fatal symptoms of the coronavirus. These include patients with comorbidities, above the age of 60 years and people at risk of contracting large viral loads, such as healthcare providers caring for critical admissions in in-patient wards, Intensive Care Units and Emergency Room settings.

Summary: Many different vaccine strategies are under development throughout different stages of the research timeline; however, it is estimated that none will show favorable results before end of 2020. For any immunization or interventional prevention/therapy system to reach the public and patients at high risk, it needs to undergo multiple phase trials to ensure safety and effectiveness. In this scoping review we aim to map the literature on COVID-19 vaccines and provide recommendations related to gaps in research, applicability and expected challenges for implementation of nationwide vaccination in Saudi Arabia.

1. Introduction

The novel coronavirus is a respiratory illness that originated in China in late 2019. (MoH, 2020) The disease is characterized by symptoms ranging from acute respiratory distress, pneumonia, to flu-like symptoms and even asymptomatic disease states in many patients. It was initially referred to as novel coronavirus disease (nCoV), but in February 2020 the World Health Organization (WHO) named it COVID-19 (Who, 2020) The causative virus is a corona virus known as SARS-CoV-2. The virus originated in Wuhan,

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China and was first observed by the local health authorities after observing the increasing cases of viral pneumonia in patients visiting specific wet markets selling bats in Wuhan. (Lau et al., 2005) The disease spread from towns to cities to different countries, and human to human spread of the virus became the primary route of transmission within 3 months of onset; and by March 2020, the World Health Organization declared COVID-19 as a global pandemic. The major route of transmission is droplets that are aerosolized while coughing, sneezing or talking. However, the possibility of airborne transmission is also widely being discussed in literature. (Zhang et al., 2020) (See Table 1.)

As of 30th September 2020, available global online databases show 188 countries around the world being affected by the virus and reported 33,692,221 number of individual cases and a total of 1,008,842 fatalities. Saudi Arabia alone confirmed 334,187 cases with a death toll of 4739. (Johns Hopkins Coronavirus Resource Center, 2020) The diseases onset of symptoms were carefully observed in vulnerable population groups, and statistics showed that elderly patients with comorbidities (Jain and Yuan, 2020) and healthcare professionals, (Smith, 2020) were at a greater risk of mortality and disease transmission than the rest of the population to whom vaccination is equally important.

The role of vaccines in prevention of viral infections has been emphasized widely for years with a great deal of research still ongoing for the development of different kinds of vaccines. (Oh, Lee and Shin, 2019) The release of the virus's genetic sequence helped several research labs get a head start on their vaccine trials; many of which are building upon their previous efforts to develop a SARS-CoV-1 and MERS-CoV vaccines (Vabret et al., 2020) Although the journey to find and implement an effective and safe vaccine strategy will take over months to years, many research groups are trying to accelerate their trials due to the impact of the pandemic.

The Kingdom of Saudi Arabia has a high burden of chronic diseases such as diabetes, hypertension, cardiovascular diseases, respiratory illnesses and cancer. (Alqahtani et al., 2020) Healthcare providers dealing directly with COVID-19 patients are at higher risk of exposure to large viral loads, making them a priority once an effective and safe vaccine is available. (Friese et al., 2020) This scoping review aims to discuss the current knowledge of SARS-CoV-2 vaccine candidates in clinical development with a focus on the current challenges and opportunities in Saudi Arabia for such vaccines. We conducted a literature search via PubMed, Medline™, and Google scholar using the keywords: COVID-19, SARS-COV2, corona, vaccine, immunization combined and separately.

2. Coronavirus vaccine technologies

The coronavirus is spherically shaped with a distinct composition of spike proteins, particularly the highly N-glycosylated spike protein (S) which varies in each type of coronavirus. This spike protein S protrudes from the surface of the virus giving it a crown-like appearance. (Beniac et al. (2006)) The spike binds to human cells, allowing access to the virion gaining entrance into the host, facilitating in receptor binding and structural support. The virus consists of a positive-sense single-strand RNA and a host cell derived glycoprotein envelop with spikes (ProSci, 2020).

Coronaviruses come under a group of viruses that use messenger RNA (mRNA) for replication inside the host cell and are divided into alpha, beta, gamma and delta subcategories. The betacoronaviruses have caused recent pandemics which affected both animals and humans Lefkowitz et al. (2018). Although SARS-CoV-2 is known to be less pathogenic than the other coronaviruses that have caused outbreaks, it has a high transmission rate (Rabaan et al., 2020).

Extensive research is being condensed to bring a COVID-19 vaccine by late 2020 or early 2021, as well testing the vaccine safety to prevent any form of immunopotentiation, be it eosinophilic infiltration or increased infectivity.

Table 2 shows on-going COVID-19 vaccination research projects which have entered clinical trials throughout the world; some of which plan to publish results by the end of 2020, while others might not complete phase III clinical trials until 2024. Table 2 categorizes the various development approaches taken for the SARS-CoV-2 vaccine. A few other techniques are being applied include, traditional inactivated virus vaccines, adenovirus vectors, mRNA - based vaccines, DNA vaccines, protein vaccines and one project using oral delivery of plasmids containing S-protein via live bacteria Thanh Le et al. (2020).

Ad5-nCoV vaccine candidate, developed by CanSino Biologics in China, has recently shown success with their two vaccine doses undergoing Phase-III safety studies. Both groups of vaccinated participants developed neutralizing antibody responses in 47–59% of the volunteers and seroconversion of binding antibodies in 96–97% of them (Zhu et al., 2020).

Another vaccine candidate, the **ChAdOx1 nCoV19 (AZD1222)** adenovirus vector vaccine developed by the University of Oxford in the United Kingdom, was tested for safety and efficacy. They used the meningococcal conjugate vaccine (MenACWY) as a control and the homologous boosting sessions showed increases in humoral and cellular immune responses in participants. The most prominent adverse effects were pain and tenderness on site of injection with and without paracetamol (Folegatti et al. (2020)).

The American Biotechnology company, Moderna, Inc. is in process of developing the mRNA**-1273** vaccine**.** This vaccines is made with potent lipid nanoparticle dispersion containing mRNA encoding for the SARS-CoV-2 spike protein. The rapid manufacturing of this vaccine made it to the first-in-human clinical trials. Moreover, vaccine development timelines were condensed to two to six months after receiving their Fast Track Designation mid-May

Table 1
Differences between the SARS-CoV-1, SARS CoV-2, MERS-CoV. (Rabaan et al., 2020) [1].

	SARS-CoV-1 (2002)	MERS-CoV (2012)	SARS-CoV-2 (2020)
Origin	China	Saudi Arabia	China
Disease Mechanism	Binds to ACE-2 receptor	Binds to Dipeptidyl peptidase-4 (DPP4) receptor	Binds to ACE-2 receptor
Source/Vector	Bats	Bats Camels	Bats
Reproductive Number (R_0)	1.7 – 1.9	0.7	2–2.5
Transmission	Human to human contact	Mainly Ingestion	Ingestion, human to human contact
Genetic Similarity	No significant similarities between SARS-CoV-1 and MERS-CoV		– 79% similar to SARS-CoV-1 – 50% similar to MERS-CoV
Genetic Differences	Longer S-protein	–	Presence of furin like cleavage site

[1] Rabaan, A. A. et al. (2020) 'SARS-CoV-2, SARS-CoV, and MERS-COV: A comparative overview', Le infezioni in medicina.

Table 2
Current COVID-19 Vaccines in Clinical Trials.

Technology	Vaccine Candidate	Country	Mechanism	Trial Phase	Duration	Sponsor
Reconstructed Old Vaccines	Bacillus Calmette-Guerin (BCG) Vaccine (NYTimes, 2020)	Australia	Vaccinating human volunteers with BCG vaccine (protection against SARS-CoV-2)	Phase-III	23rd March 2020 – July 2020	Murdoch Children's Research Institute
	CoronaVac (PicoVac) (Medicine, 2020b)	China	Inactivated SARS-CoV-2 virus technology for COVID-19 prophylaxis	Phase III	16th April 2020 – 13th December 2020	SinoVac Biotech Ltd.
	Unspecified (NCT04412538, 2020)	China	Inactivated SARS-CoV-2 virus technology for COVID-19 prophylaxis	Phase I Phase II	15th May 2020 - September 2020	Chinese Academy of Medical Sciences
Attenuated Virus Vaccines	Unspecified (Pneumonia Vaccine) (Xia and Chen, 2020)	China	Inactivated Novel Coronavirus Pneumonia vaccine (Vero cells)	Phase III	11th April 2020–90-360 days	Wuhan Institute of Biological Products co., LTD.
	CDX-005 (CDX-CoV) (Codagenix, 2020)	UAE	Inactivated SARS-CoV-2 virus technology for COVID-19 prophylaxis	Phase-III	15th April – Late 2020	SinoPharm
	Unspecified (The National, 2020)· (Globaltimes.cn, 2020)	China	Recombinant adenovirus type-5 (Ad5) vector expressing SARS-CoV-2 spike glycoprotein	Phase-II	16th March 2020 - end of 2020	CanSino Biologics Inc.
	Ad5-nCoV (Inc. *et al.*, 2020)	United Kingdom	Nonhuman (chimpanzee) adenovirus vector	Phase-III	23rd April 2020 – end of 2020	AstraZeneca University of Oxford
	ChAdOx1 nCoV19 (NCT04324606, 2020)	China	Covid-19 minigenes engineered based lentiviral vector system (NHP/TYF)	Phase-I	February 2020 – 31st December 2024	Shenzhen Geno-Immune Medical Institute
	COVID-19/aAPC (Clinical Trials, 2020)	China	Covid-19 minigenes engineered based on lentiviral vector system (NHP/TYF)	Phase-I Phase-II	24th March 2020 – 31st December 2024	Shenzhen Geno-Immune Medical Institute
	Gam-COVID-Vac Lyo (clinical trials, 2020)	Russia	Non-replicating Adenovirus Ad5 and Ad26 combination vector	Phase-III	16th June 2020 – end of 2020	Gamaleya Research Institute of Epidemiology and Microbiology, Russian Ministry of Heath
	Ad26.COV2-S (Ad26COVS1) (JNJ-78436735)	United States	Recombinant adenovirus vector using Janssen's AdVac® technology	Phase-III	January 2020 – end of 2020	Johnson & Johnson
Viral Vector Vaccines	Ad26.COV2-S (Johnson & Johnson)	United States	Recombinant vesicular stomatitis virus (rVSV)	Preclinical	May 2020–2021	Merck & IAVI
	rVSVΔG-SARS-CoV-2 (iavi, 2020)	United States	Adeno-associated Virus (AAV) vector technology	Preclinical	28th May 2020 – late 2020	Novartis, Massachusetts General Hospital and Massachusetts Eye and Ear
	AAVCOVID (STAT, 2020)	United States	Using genetically modified measles viruses delivering portions of SARS-CoV-2 into host	Preclinical	26th May 2020 -	Merch, Themis Bioscience
	Measles Virus Vector (Themisbio, 2020)	United States	mRNA Lipid Nanoparticles	Phase-III	13th May 2020 – end of 2020	ModernaTX, Inc.
	mRNA-1273 (NCT04405076, 2020)	United States, Germany	SARS-CoV-2 RNA vaccine for COVID-9 prophylaxis	Phase-III	29th April 2020-end of 2020	Pfizer, BioNTech, Fosun Pharma
RNA-Based Vaccines	BNT162 (a1, b1, b2, c2) (NCT04368728, 2020)	United Kingdom	mRNA mimicking viral genes for spike protein	Phase-I	April 2020 - July 2021	Imperial College London
RNA-Based Vaccines	LNP-nCoVsaRNA (Isrctn, 2020)	Germany	mRNA technology	Phase-II	March 2020 – unspecified end date	CureVac
	CureVac (CureVac, 2020)	China	SARS-CoV-2 mRNA vaccine	Phase-	June 2020-unspecified end date	People's Liberation Army (PLA) Academy of Military Sciences
DNA-Based Vaccines	ARCoV (News.cgtn, 2020)	Republic of Korea	DNA Plasmid: intradermal injection electroporation (EP) via CELLECTRA® 2000 device technology	Phase-I	3rd April 2020 – July 2021	Inovio Pharmaceuticals
	INO-4800 (Medicine, 2020a)	Republic of Korea	DNA Vaccine for COVID-19 Prophylaxis	Phase-I Phase-II	17th June 2020 – 17th June 2022	Genexine, Inc.
	GX-19 (Clinicaltrials, 2020)	Australia	Recombinant nanoparticle SARS-CoV-2 vaccine (Matrix-M adjuvant)	Phase-I/II	25th May 2020 – end of 2020	Novavax
	NVX-CoV2373 (NCT04368988, 2020)	Australia	Recombinant SARS-CoV-2 Trimeric S Protein Subunit Vaccine	Phase-I	19th June 2020 – 30th March 2021	Clover Biopharmaceuticals, GlaxoSmithKline Sanofi
	SCB-2019 (NCT04405908, 2020)	United States	Oral tablet recombinant adenovirus protein delivering COVID-19 genes	Phase-II	31st January 2020 – unspecified end date	Vaxart, Inc.
Protein Vaccines	Oral recombinant VAAST (Martin, 2020) (Precision vaccinations, 2020)	China	Combination of viral proteins + adjuvant	Phase-I	February 2020-Unspecified	Anhui Zhifei Longcom Biopharmaceutical Co. Ltd.
	Adjuvanted recombinant protein (CovidVax, 2020)	United States	Reviving SARS-Cov-1 Project	Phase-I	April 2020 + 18 months	Baylor College of Medicine, Texas Children's Hospital

(*continued on next page*)

Table 2 (*continued*)

Technology	Vaccine Candidate	Country	Mechanism	Trial Phase	Duration	Sponsor
Engineered Bacterial Vaccine	CoV RBD219-N1 (Coronavirus Vaccines, 2020)[2]	Canada	Orally delivered: S-Protein coding plasmid delivery via engineered bacteria	Phase-I	March-[t] August 2021	Symvivo Corporation

[2]Baylor College of Medicine. 2020. Coronavirus Vaccines. [online] Available at: https://www.bcm.edu/departments/pediatrics/sections-divisions-centers/tropical-medicine/research/vaccine-development/coronavirus-vaccines [Accessed 23 August 2020].
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2020. The phase-II trial of the mRNA-1273 vaccine helped in successfully detect high neutralizing antibody responses which increased in a dose-dependent manner Jackson et al. (2020).

On the other hand, the **Gam-COVID-Vac-Lyo** vaccine being developed in Russia has completed the collection of primary outcome measures by August 2020. However, Russian authorities have decided to grant this vaccine an emergency use authorization despite the fact that phase III clinical trials have not been completed.

3. Current challenges of vaccine development

A proposed solution to a fast and effective vaccine development strategy, to reach human trials within 3 to 6 months, includes enrolling participants from regions where COVID-19 is at a rise. This will allow sufficient enrollment of all vaccines and rapid collection of data, where a combined placebo group is proposed along with international collaboration of all the researches simultaneously to reach diverse regions around the world (Lurie et al., 2020).

Nevertheless, endeavors of vaccine research come along with various obstacles that scientists must face during the development. A recent study discussed the decay in anti-SARS-CoV-2 IgG antibodies in patients suffering mild symptoms of COVID-19, posing a challenge to vaccine development for the attenuated virus vaccine research groups. The study involved 34 participants and their Log_{10} Anti-RBD IgG (ng/mL) was measured twice, against the days of symptom onset. The first measurement was made after 37 days of onset of symptoms and the second measurement took place after 86 days of onset of symptoms. It concluded that antibodies levels decreased rapidly within 3 months from onset of symptoms. This study raised concerns about humoral immunity against COVID-19 as a target for vaccine development which adds an additional challenge (Ibarrondo et al., 2020). The other phase-II clinical trials showed T-cell response in 90% of participants while 85% generated neutralizing antibodies, and also indicated that patients older than 55 years had lower antibody titer when tested during the study. This vulnerable population group may pose a new challenge to ongoing SARS-CoV-2 vaccine research (Zhu et al., 2020). Another recent study has shown compelling outcomes after evaluating the SARS-CoV-2 specific memory T-cells in convalescent patients and participants exposed to COVID-19. Cytotoxic phenotypes were represented in the acute phase T-cells, however, the convalescent phase T-cells exhibited polyfunctional stem-like memory (Sekine et al., 2020).

Other challenges include Antibody-Dependent Enhancement (ADE) and Vaccine-Associated Enhanced Respiratory Disease (VAERD). ADE is a disease enhancement phenomenon which aids in antibodies assisted viral entry into the host cell (Bramhachari, n.d.) This allows the virus to replicate and exacerbate infection increasing its virulence and infectivity. ADE halted previous efforts to develop a vaccine against SARS-CoV-1 and MERS-CoV in animal studies; however, they are not yet confirmed challenges in humans. VAERD is a mechanism that was seen in a vaccine trial in children given inactivated virus vaccines against the respiratory Syncytial virus (RSV), which enhanced low respiratory tract infection symptoms in the children (Rajão et al., 2016). VAERD was also reported in children during the measles virus research trials using alum adjuvants in attenuated live virus vaccines. These alum adjuvants are still being used in many of the attenuated virus vaccine candidates (Xia et al., 2020).

Another challenge is immunization strategies in each county. It is known that some patient populations are vulnerable to developing serious disease and fatal complications including older adults and patients with underlying disorders, pregnant women, patients on immunosuppressant therapy, or immunocompromised secondary to disease or infection (Maltezou and Poland, 2016). Another category of potential vaccine candidate target is healthcare professionals who are at higher risk of acquiring COVID-19. It is important to develop a national immunization strategy that addresses the needs of individual or specific country according to several factors including availability, supply, and high-risk population.

4. Implications in Saudi Arabia

Saudi research attempts to utilize lessons learned from developing a MERS-CoV vaccine into creating a COVID-19 vaccine in universities and research centers nationwide. On a side note, the Saudi Ministry of Health announced its collaboration with CanSino Biologics, the Chinese vaccine company after they successfully conducted phase I/II trials within China. CanSino may be conducting their phase-III clinical trial in Saudi Arabia where they aim to recruit 5,000 adult subjects. Moreover, according to Russian Direct Investment Fund (RDIF) spokesman, the **Gam-COVID-Vac-Lyo** vaccine being developed in Moscow, Russia, may be conducting their phase-III clinical trial in Saudi Arabia among other countries as well (Arab News, 2020).

One of the main challenges is the fast access to safe, effective and affordable vaccines. In Saudi Arabia, the Saudi Food and Drug Authority (SFDA) is responsible for the evaluation and approval of medicinal products in the country. Regulatory agencies, including the SFDA, are expected to grant priority or fast-track application processes in order to expedite the COVID-19 vaccine candidate approval, given that safety and efficacy are evidently proven.

Large amount of governmental funding from North American and European countries has been awarded to several potential vaccines candidates that showed early positive results such as Moderna, Johnson & Johnson, AstraZeneca and The Gamaleya Research Institute, part of Russia's Ministry of Health. The collective goal of these companies is to deliver 300 million doses of an effective COVID-19 vaccine by January 2021.

It is expected to have high demand of the first approved vaccine and no company can meet the required supply alone. One of the main challenges for Saudi Arabia is early access to adequate supply of the vaccine to the country's large population. Therefore, to ensure this, AstraZeneca has signed a number of agreements with international organizations such as the Global Alliance for Vaccines and Immunization (GAVI), Coalition for Epidemic Preparedness Innovations (CEPI), and the WHO to manage, allocate, purchase and distribute the vaccine worldwide. This will be conducted through the Access to COVID-19 Tools (ACT) accelerator program. This program aims to raise around $750 millions for the manufacturing, purchase and distribution of 300 million doses worldwide. Saudi Arabia has contributed $150 millions towards this program which should allow priority access to some supply. In addition, AstraZeneca has signed an agreement with the Serum Institute of India, which aims to produce one billion doses of the candidate vaccine for global distribution, 400 million of which could be available before the end of 2020.

Furthermore, previous epidemics such as SARS and Zika, ended before the vaccines were available, leaving vaccine companies in financial crisis after the funds provided were redistributed. This may be a challenge for vaccine researches if COVID-19 cases plummet before a vaccine is available in the market. (NEJM, 2020)

The expected price of the vaccine is $5–37 per dose depending on the type and manufacturer of the vaccine. (Loftus, 2020) Expecting that each person may need two doses to achieve targeted protection, the vaccine will potentially cost between $10–74 per person. This translates into SR1.3 billion to SR 9.6 billion budget impact inflation to cover the Saudi population.

Another challenge in Saudi Arabia is the immunization strategy to quickly cover the entire population. Implementation of vaccine administrators in retail pharmacies will allow majority of the population to be immunized against COVID-19 (Yemeke et al., 2020). Another study showed that the availability of immunization programs in local pharmacies increased the population seeking vaccines for viral infections (Isenor et al., 2016). Implementation of a similar strategy against the influenza vaccine was established by Saudi Arabia's local pharmacies a few years ago and showed positive results. (Saudi Gazette). This was recently proposed by the Saudi Society of Clinical Pharmacy (Badreldin et al., 2020).

5. Conclusion

The COVID-19 pandemic has impacted every country in the world. Developing an effective, safe and affordable vaccine is an important strategy to fight this pandemic. There are several vaccine candidates in clinical trials currently with the soonest expected to reach the market during late 2020. Out of the numerous challenges in Saudi Arabia, including securing enough supply

and affordability of this vaccine, early access to a safe and effective vaccine with the development of appropriate immunization strategy are key factors to overcome this pandemic in Saudi Arabia.

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Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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