Review

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

AlAnoud TofailAhmed Raja a, Aws Alshamsan b, Ahmed Al-jedai c

a College of Pharmacy, Alfaisal University, Riyadh, Saudi Arabia
b Nanobiotechnology Unit, Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
c Therapeutic Affairs, Ministry of Health, Saudi Arabia

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.

© 2020 The Authors. Published by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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 outbreaks, it has a high transmission rate (Rabaan et al., 2020). 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, adenorvirus 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) adenorvirus 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.

| Origin | SARS-CoV-1 (2002) | MERS-CoV (2012) | SARS-CoV-2 (2020) |
|--------|------------------|-----------------|------------------|
| Disease Mechanism | China | Saudi Arabia | China |
| Source/Vector | Bats | Binds to Dipeptidyl peptidase-4 (DPP4) receptor | Binds to ACE-2 receptor |
| Reproductive Number (R0) | 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 | 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.
| Technology                     | Vaccine Candidate                  | Country                  | Mechanism                                                                 | Trial Phase                  | Duration                     | Sponsor                                                                 |
|-------------------------------|------------------------------------|--------------------------|---------------------------------------------------------------------------|----------------------------|------------------------------|--------------------------------------------------------------------------|
| Reconstructed Old Vaccines    | Bacillus Calmette-Guerin (BCG)     | 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)                | 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                     | 15th May 2020 – September 2020 | Chinese Academy of Medical Sciences                                      |
|                               | Unspecified (Pneumonia Vaccine)    | 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                                                                |
| Attenuated Virus Vaccines     | Unspecified (The National, 2020)   | China                    | Recombinant adenovirus type-5 (Ad5) vector expressing SARS-CoV-2 spike glycoprotein | Phase-II                    | 16th March 2020 – end of 2020 | CanSino Biologies Inc.                                                    |
|                               | Ad5-nCoV (Inc. et al., 2020)       | China                    | Nonhuman (chimpanzee) adenovirus vector                                   | Phase-III                   | 23rd April 2020 – end of 2020 | AstraZeneca University of Oxford                                           |
|                               | ChAdOx1 nCoV19 (NCT03424606, 2020)| China                    | Covid-19 minigenes engineered based lentiviral vector system (NHP/TF)     | Phase-I                     | February 2020 – 31st December 2024 | Shenzhen Geno-Immune Medical Institute                                   |
|                               | COVID-19/JaPAC (Clinical Trials, 2020)| China                  | Covid-19 minigenes engineered based on lentiviral vector system (NHP/TF) | Phase-I/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 Health Johnson & Johnson |
|                               | Ad26.COVID-S (Ad26COV51) (JN-78436735) | United States       | Recombinant adenovirus vector using Janssen’s AdVac® technology          | Phase-III                   | January 2020 – end of 2020    | Merck & IAV                                                               |
| Viral Vector Vaccines         | Ad26.COVID-2S (Johnson & Johnson)  | United States           | Recombinant vesicular stomatitis virus (VSV)                              | Preclinical                 | May 2020–2021                | Novartis, Massachusetts General Hospital and Massachusetts Eye and Ear     |
|                               | rSVA-VACS-CoV2 (iav, 2020)         | United States           | Adeno-associated Virus (AAV) vector technology                            | Preclinical                 | 28th May 2020 – late 2020    | Merch, Themis Bioscience                                                  |
|                               | AAVCOVID (STAT, 2020)              | United States           | Using genetically modified measles viruses delivering portions of SARS-CoV-2 into host mRNA Lipid Nanoparticles | Preclinical                 | 26th May 2020 –               | ModernaTX, Inc.                                                           |
| RNA-Based Vaccines            | Measles Virus Vector (Themisbio, 2020) | United States       | SARS-CoV-2 RNA vaccine for COVID-19 prophylaxis                           | Phase-III                   | 13th May 2020 – end of 2020   | Pfizer, BioNTech, Fosun Pharma                                            |
| DNA-Based Vaccines            | mRNA-1273 (NCT043403706, 2020)     | United States           | mRNA mimicking viral genes for spike protein                              | Phase-I                     | 17th June 2020 – 30th March 2021 | Clover Biopharmaceuticals, GlaxoSmithKline Sanofi Vaxart, Inc.            |
|                               | BNT162 (j1, b1, b2, c2) (NCT04368728, 2020) | United States       | mRNA mimicking viral genes for spike protein                              | Phase-I                     | 17th June 2020 – 30th March 2021 | Clover Biopharmaceuticals, GlaxoSmithKline Sanofi Vaxart, Inc.            |
|                               | LNP-nCoVArRNA (Isrctn, 2020)       | United States           | mRNA mimicking viral genes for spike protein                              | Phase-I                     | 17th June 2020 – 30th March 2021 | Clover Biopharmaceuticals, GlaxoSmithKline Sanofi Vaxart, Inc.            |
|                               | CureVac (CureVac, 2020)            | China                    | SARS-CoV-2 mRNA vaccine                                                   | Phase-I                     | June 2020 – unspecified end date | People’s Liberation Army (PLA) Academy of Military Sciences              |
|                               | ARCoV (News.cgtn, 2020)            | Republic of Korea       | DNA Plasmid: intradermal injection electrorepportion (EP) via CELLECTRA®   | Phase-I                     | 3rd April 2020 – July 2021   | Inovio Pharmaceuticals                                                    |
|                               | ONO-4800 (Medicine, 2020a)         | Republic of Korea       | DNA Vaccine for COVID-19 Prophylaxis                                      | Phase-I/II                  | 17th June 2020 – 25th May 2020 | Genexine, Inc.                                                           |
|                               | GJ-19 (Clinicaltrials, 2020)       | Australia                | Recombinant nanoparticle SARS-CoV-2 vaccine (Matrix-M adjuvant)            | Phase-I                     | 19th June 2020 – 30th March 2021 | 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 Vaxart, Inc.            |
|                               | SCR-2019 (NCT04405908, 2020)       | United States           | Oral tablet recombinant adenovirus protein delivering COVID-19 genes       | Phase-II                    | 31st January 2020 – unspecified end date | Anhui Zhifei Longcom Biopharmaceutical Co. Ltd.                           |
|                               | Oral recombinant VAAST (Martin, 2020) | China                    | Combination of viral proteins + adjuvant                                 | Phase-I                     | February 2020 – Unspecified  | Baylor College of Medicine, Texas Children’s Hospital                    |
|                               | 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, 2021 | Synmivac Corporation |

²Baylor 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].

Clinicaltrials.gov. 2020. An Open Study of The Safety, Tolerability And Immunogenicity Of “Gam-COVID-Vac Llo” Vaccine Against COVID-19 - Tabular View - Clinicaltrials. Gov. [online] Available at: https://www.clinicaltrials.gov/ct2/show/record/NCT04437875 [Accessed 23 August 2020].

Clinicaltrials.gov. 2020. Safety and Immunogenicity Study Of CX-19, A COVID-19 Preventive DNA Vaccine In Healthy Adults - Tabular View - Clinicaltrials.Gov. [online] Available at: https://www.clinicaltrials.gov/ct2/show/record/NCT04445389 [Accessed 23 August 2020].

Codagenix, L. 2020. Codagenix Announces The Synthesis And Preliminary Safety Of Scalable, Live-Attenuated Vaccine Candidate Against COVID-19. [online] Prenswire.com. Available at: https://www.prenswire.com/news-releases/codagenix-announces-the-synthesis-and-preliminary-safety-of-scalable-live-attenuated-vaccine-candidate-against-covid-19-301079306.html [Accessed 23 August 2020].

Contre Lab. U.S. 2020. Johnson & Johnson Announces A Lead Vaccine Candidate For COVID-19; Landmark New Partnership with U.S. Department Of Health & Human Services; And Commitment To Supply One Billion Vaccines Worldwide For Emergency Pandemic Use | Johnson & Johnson | [online] Available at: https://www.jnj.com/johnson-johnson-announces-a-lead-vaccine-candidate-for-covid-19-landmark-new-partnership-with-u-s-department-of-health-human-services-and-commitment-to-supply-one-billion-vaccines-worldwide-for-emergency-pandemic-use [Accessed 23 August 2020].

Covidvax.org. 2020. COVID-19 Vaccine: RBD-Dimer by Anhui Zhifei Longcom Biopharma, Institute of Microbiology Chinese Academy Of Sciences. [online] Available at: https://www.covidvax.org/covid19-vaccine/AnhuiZhifei/Adjuvanted-recombinant-protein-Anhui-Zhifei-Longcom-Biopharmaceutical-Institute-of-Microbiology-Chin [Accessed 23 August 2020].

Curevac.com. 2020. CureVac’s Optimized mRNA Platform Provides Positive Pre-Clinical Results at Low Dose For Coronavirus Vaccine Candidate – CureVac. [online] Available at: https://www.curevac.com/en/2020/05/14/curevacs-optimized-mrna-platform-provides-positive-pre-clinical-results-at-low-dose-for-coronavirus-vaccine-candidate/ [Accessed 23 August 2020].

Globaltimes.cn. 2020. Chinese COVID-19 Vaccine Candidate the First to Start Phase 3 Clinical Trials Worldwide - Global Times. [online] Available at: https://www.globaltimes.cn/content/1192598.shtml [Accessed 23 August 2020].

Iavi.org. 2020. [online] Available at: https://www.iavi.org/phocadownload/iavi_fact_sheet_coronavirus-vaccine-program.pdf [Accessed 23 August 2020].

Inc., C. B. et al. 2020. ‘Phase I Clinical Trial of a COVID-19 Vaccine in 18–60 Healthy Adults’, ClinicalTrials. Institute, S. G.-L. M. 2020. Immunity and Safety of Covid-19 Synthetic Mimgene Vaccine’, ClinicalTrials.gov. 2020. ISRCTN17072002: Clinical Trial To Assess The Safety Of A Coronavirus Vaccine In Healthy Men And Women. [online] Available at: https://www.isrctn.com/ISRCTN17072092 [Accessed 23 August 2020].

Medicine, U. N. L. 2020a. Safety, Tolerability and Immunogenicity of INO-4800 for COVID-19 in Healthy Volunteers, Clinicaltrials.gov. Medicine, U. N. L. 2020b. Safety and Immunogenicity Study of Inactivated Vacci ne for Prophylaxis of SARS-CoV-2 Infection (COVID-19), ClinicalTrials.gov. 2020. MI-euglobehosnewsire.com. [online] Available at: https://mi-euglobehosnewsire.com/Resource/Download/d77e80a4-4145-4c7e-9f3d7-94d54749a50 [Accessed 23 August 2020].

NCT04324606 (2020) ‘A Study of a Candidate COVID-19 Vaccine (COV001)’, [online] Available at: https://clinicaltrials.gov/show/NCT04324606 [Accessed 23 August 2020].

NCT04334980 (2020) ‘Evaluation of the Safety and Immunogenicity of INO-4800 for COVID-19 in Healthy Volunteers’, [online] Available at: https://clinicaltrials.gov/show/NCT04334980 [Accessed 23 August 2020].

NCT04334988 (2020) ‘Study to describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults’, [online] Available at: https://clinicaltrials.gov/show/NCT04334988 [Accessed 23 August 2020].

NCT04368988 (2020) ‘Evaluation of the Safety and Immunogenicity of a SARS-CoV-2 rS (COVID-19) Nanoparticle Vaccine With/Without Matrix-M Adjuvant’, [online] Available at: https://clinicaltrials.gov/show/NCT04368988 [Accessed 23 August 2020].

NCT04405076 (2020) ‘Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 COVID-19 Vaccine in Adults Aged 18 Years and Older’, [online] Available at: https://clinicaltrials.gov/show/NCT04405076 [Accessed 23 August 2020].

NCT04405908 (2020) ‘A Phase 1 Study of SCB-2019 for COVID-19 in Healthy Volunteers’, [online] Available at: https://clinicaltrials.gov/show/NCT04405908 [Accessed 23 August 2020].

NCT04412538 (2020) ‘Safety and Immunogenicity Study of an Inactivated SARS-CoV-2 Vaccine for Preventing Against COVID-19’, [online] Available at: https://clinicaltrials.gov/show/NCT04412538 [Accessed 23 August 2020].

NCT04412538 (2020) ‘Safety and Immunogenicity Study of an Inactivated SARS-CoV-2 Vaccine for Preventing Against COVID-19’, [online] Available at: https://clinicaltrials.gov/show/NCT04412538 [Accessed 23 August 2020].

News.cgtncn.com. 2020. China’s First COVID-19 mRNA Vaccine Approved for Clinical Trials. [online] Available at:https://news.cgtncn.com/news/2020–06-26/China-s-first-COVID-19-mRNA-vaccine-approved-for-clinical-trials-RDTXX0jVJK/index.html [Accessed 23 August 2020].

Nytimes.com. 2020. Can an Old Vaccine Stop the New Coronavirus? [online] Available at: https://www.nytimes.com/2020/04/03/health/coronavirus-bcg-vaccine.html [Accessed 23 August 2020].

Precisionvaccinations.com. 2020. First Oral COVID-19 Vaccine Selected for Operation Warp Speed. [online] Available at: https://www.precisionvaccinations.com/first-oral-covid-19-vaccine-selected-operation-warp-speed [Accessed 23 August 2020].

Safety and Immunity of Covid-19 aAPC Vaccine’, (2020) [online] Available at: https://www.learner.org/lc/25029/25029.html [Accessed 23 August 2020].

STAT. 2020. Big Gene Therapy Names Line Up Behind Experimental COVID-19 Vaccine. [online] Available at: https://www.statnews.com/2020/05/28/big-gene-therapy-names-line-up-behind-experimental-covid-19-vaccine/ [Accessed 23 August 2020].

The National. 2020. Coronavirus: UAE And China to Join Forces in New Vaccine Trial. [online] Available at: https://www.thenational.ae/uae/news/coronavirus-uae-and-china-to-join-forces-in-new-vaccine-trial-1.1038163 [Accessed 23 August 2020].

Themisbio.com. 2020. [online] Available at: https://www.themisbio.com/wp-content/uploads/2020/05/Msd-and-Themis-News-Release–5–26-2020-Final_ENG.pdf [Accessed 23 August 2020].

Xia, S. and Chen, W. (2020) A randomized, double-blind, placebo parallel-controlled phase I/II clinical trial for inactivated Novel Coronavirus Pneumonia vaccine {Vero cells’}, Actas Urológicas Españolas.

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 immunologists 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 (Brambchari, 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 vaccination (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 (Badredin 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.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

References

Alqahtani, S., Aljumah, A., Hashim, A., Alenazi, T., Aljawad, M., Al Hamoudi, W., Alghamdi, M., 2020. Principles of Care for Patients with Liver Disease During the Coronavirus Disease 2019 (COVID-19): Pandemic. Position Statement of the Saudi Association for the Study of Liver Disease and Transplantation. Annals Saudi Medicine 40 (4), 273–280.

Arab News. 2020. Russian Coronavirus Vaccine Trials To Be Held In Saudi Arabia. [online] Available at: <https://www.arabnews.com/node/1705691/saudi-arabia> [Accessed 20 August 2020].

Badreddin, H.A. et al., 2020. Pharmacists roles and responsibilities during epidemics and pandemics in Saudi Arabia: An opinion paper from the Saudi Society of Clinical Pharmacy. Saudi Pharmaceutical Journal 28, 1030–1034.

Beniac, D.R. et al., 2006. Architecture of the SARS coronavirus prefusion spike. Nat. Struct. Mol. Biol. https://doi.org/10.1038/nsmb1123.

Bramhachari, P., n.d. Dynamics Of Immune Activation In Viral Diseases.

Folegatti, P.M. et al., 2020. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. The Lancet. https://doi.org/10.1016/s0140-6736(20)31604-4.

Friese, C.R. et al., 2020. Respiratory Protection Considerations for Healthcare Workers during the COVID-19 Pandemic. Health Security. https://doi.org/10.1089/fs.2020.0036.

Ibarrozo, F.J. et al., 2020. Rapid Decay of Anti–SARS-CoV-2 Antibodies in Persons with Mild Covid-19. N. Engl. J. Med. https://doi.org/10.1056/nejmc2025179.

Isenor, J.E. et al., 2016. Impact of pharmacists as immunizers on vaccination rates: A systematic review and meta-analysis. Vaccine. https://doi.org/10.1016/j.vaccine.2016.08.085.

Jackson, L.A. et al., 2020. An mRNA Vaccine against SARS-CoV-2 — Preliminary Report. N. Engl. J. Med. https://doi.org/10.1056/nejmoa2022483.

Jain, V., Yuan, J., 2020. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int. J. Public Health 65 (5), 533–546.

Johns Hopkins Coronavirus Resource Center. 2020. COVID-19 Map – Johns Hopkins Coronavirus Resource Center. [online] Available at: <https://coronavirus.jhu.edu/map.html> [Accessed 24 August 2020].

Lau, S. K. P. et al. (2005) ‘Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats’, Proceedings of the National Academy of Sciences of the United States of America. doi: 10.1073/pnas.0506735102.

Lee, S.H., 2020. A dangerous rush for vaccines. Science. https://doi.org/10.1126/science.abe3147.

Lurie, N. et al., 2020. Developing covid-19 vaccines at pandemic speed. N. Engl. J. Med. https://doi.org/10.1056/NEJMp2005630.

Maltezou, H., Poland, G., 2016. Immunization of Health-Care Providers: Necessity and Public Health Policies. Healthcare. https://doi.org/10.3390/healthcare4030047.

Moh, 2020. Coronavirus – Novel Coronavirus (COVID-19). [online] Moh.gov.sa. Available at: <https://www.moh.gov.sa/en/HealthAwareness/EducationalContent/Corona/Pages/corona.aspx> [Accessed 24 August 2020].

New England Journal of Medicine. 2020. Developing Covid-19 Vaccines At Pandemic Speed | NEJM. [online] Available at: <https://www.nejm.org/full/10.1056/NEJM2005630> [Accessed 24 August 2020].

Oh, S.J., Lee, J.K., Shin, O.S., 2019. Aging and the immune system: The impact of immunosenescence on viral infection, immunity and vaccine immunogenicity. Immunology Network. https://doi.org/10.4110/in.2019.1637.

Prosci-inc.com. 2020. COVID-19 | SARS-CoV-2 | 2019-Ncov Reagents - Prosci. [online] Available at: <https://www.prosci-inc.com/covid-19/> [Accessed 24 August 2020].

Rabaan, A. A. et al. (2020) ‘SARS-CoV-2, SARS-CoV, and MERS-CoV: A comparative overview’. Le infezioni in medicina.

Rajao, D., Chen, H., Perez, D., Sandbulte, M., Gauger, P., Loening, C., Shanks, G., Vincent, A., 2016. Vaccine–associated enhanced respiratory disease is influenced by haemagglutinin and neuraminidase in whole inactivated influenza virus vaccines. J. Gen. Virol. 97 (7), 1489–1499.

Sekine, T., Perez-Porti, A., Rivera-Ballesteros, O., Estrada, K., Gorin, J.B., Olsson, A., Llewellyn-Lacey, S., Kamal, H., Bogdanovic, G., Muschiol, S. and Wullimann, D.J., 2020. Robust T cell immunity in convalescent individuals with asymptomatic or mild.

Smith, C., 2020. 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. 258, 113119.

Thanthri, T. L. et al. (2020) ‘The COVID-19 vaccine development landscape’. Nature reviews. Drug development. doi: 10.1038/s41573-020-0073-5.

Vabret, N., Britton, G.J., Gruber, C., Hegde, S., Kim, J., Kuksin, M., Levantovsky, R., Malte, L., Moreira, A., Park, M.D., Pia, L., 2020. Immunology of COVID-19: current state of the science. Immunity.

WHO. 2020. Naming The Coronavirus Disease (COVID-19) And The Virus That Causes It. [online] Available at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019-technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it> [Accessed 24 August 2020].

Xia, S., Duan, K., Zhang, Y., Zhao, D., Zhang, H., Xie, Z., Li, X., Peng, C., Zhang, Y., Zhang, W., Yang, Y., 2020. Effect of an Inactivated Vaccine Against SARS-CoV-2 on Safety and Immunogenicity Outcomes: Interim Analysis of 2 Randomized Clinical Trials. JAMA.

Yemekte, T.T. et al., 2020. A systematic review of the role of pharmacists in vaccination services in low-and-middle-income countries. Res. Social Administrative Pharmacy. https://doi.org/10.1016/j.sapharm.2020.03.016.

Zhang, R., Li, Y., Zhang, A., Wang, Y., Molina, M., 2020. Identifying airborne transmission as the dominant route for the spread of COVID-19. Proc. Natl. Acad. Sci. 117 (26), 14857–14863.

Zhu, F.C. et al., 2020. Immunogenicity and safety of a recombinant adenovirus type-5–vectored COVID-19 vaccine in healthy adults aged 18 years or older; a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet. https://doi.org/10.1016/s0140-6736(20)31605-6.

Further Reading

Saudigazette. 2020. Nahdi Medical Company Joins Govt Influenza Immunization Campaign. [online] Available at: <https://saudigazette.com.sa/article/524711> [Accessed 20 August 2020].

Thorp, H.H., 2020. A dangerous rush for vaccines. Science. https://doi.org/10.1126/science.abe3147.