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Review Article

A global survey in the developmental landscape of possible vaccination strategies for COVID-19

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ABSTRACT

The development of COVID-19 vaccines was promptly regulated to ensure the best possible approach. By January 2022, 75 candidates reached preclinical evaluation in various animal models, 114 vaccines were in clinical trials on humans, and 48 were in the final testing stages. Vaccine platforms range from whole virus vaccines to nucleic acid vaccines, which are the most promising in prompt availability and safety. The USA and Europe have approved vaccines developed by Pfizer–BioNTech (BNT162b2) and Moderna (mRNA1273). So far, Pfizer–BioNTech, Moderna, Johnson & Johnson, AstraZeneca–University of Oxford, Sinopharm, Sinovac Biotech Gamaleya, Bharat Biotech, and Novavax have documented effective vaccines. Even with technological advances and a fast-paced development approach, many limitations and problems need to be overcome before a large-scale production of new vaccines can start. The Key is to ensure equal and fair distribution globally through regulatory measures. Recent studies link Bacillus Calmette–Guérin (BCG) vaccination programs and lower disease severity.

1. Introduction

COVID-19 is the disease caused by the novel coronavirus (SARS-CoV-2), which is said to have originated from a live sea-food market in Wuhan, China, somewhere around December of 2019 [1,2]. The disease has spread globally, with total positive cases estimated at over 356 million and mortality at over 5.6 million, accounting for a considerably high fatality rate (WHO data on 26 January 2022). The world community was faced with developing a safe and effective vaccine against the pandemic, emphasizing the time. Experience with SARS and MERS has proved that if the global health threat passes, vaccine development is likely to be put on hold [2,3]. Vaccine development should be guided by speed manufacturing, deployment, and global access. The Coalition for Epidemic Preparedness Innovations (CEPI), which funds the development of epidemic vaccines, in collaboration with the World Bank, set up

the COVID-19 Vaccine Development Taskforce controlling finance and global access for vaccines [4]. The greatest burden of vaccine development is in North America, with about 46%. China, the rest of Asia and Australia, and Europe account for approximately about 18% each. Currently, China has Sinopharm and Sinovac's vaccines, which so far have inoculated 243 million people. [5,6]. A total of 9 billion COVID-19 vaccine doses were being used each day worldwide, mostly in high-income countries [7]. Among the confirmed active vaccine candidates, around 72% are patented and produced by private developers, and the remaining 28% are led by academic, non-profit, and public sectors [8,9]. Even with the participation in the process of such companies as Sanofi and GlaxoSmithKline, many of the leading vaccine candidates have been developed by small manufacturers that do not have sufficient experience with large-scale manufacturing. Global coordination is key in manufacturing and meeting the demands [10]. One striking feature of

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the COVID-19 vaccine development is the various technology platforms being tested, ranging from whole virus vaccines, which are the most traditional through subunit vaccines, virus-like particles, and nucleic acid vaccines (DNA and RNA) [11,12]. Many of these are novel technologies currently not used in any licensed vaccines. This offers great flexibility in speed and antigen manipulation [10]. We have reviewed current and past literature to summarize the vaccine development scenario in the most recent times.

1.1. Previous coronavirus vaccine experiences

1.1.1. SARS

The Severe Acute Respiratory Syndrome (SARS) outbreak of 2003 originated in Guangdong, China, and affected more than 26 countries, characterized by influenza-like symptoms [13–15]. SARS was caused by the SARS-Coronavirus (SARS-CoV), which is thought to be originated from an animal reservoir such as bats, much similar to COVID-19 of 2019 [16]. Coronaviruses are broadly classified into three antigenic groups (Group 1 human coronavirus – HCoV229E, Group 2 porcine, feline and diarrhea virus FIPV, Group 3 avian virus), whereas the SARS-CoVs did not belong to any of these groups but slightly resembles Group 2. The virus probably evolved to infect humans into an early version causing localized disease and later into the SARS-CoV, which caused a global outbreak [17]. The SARS-CoV is an RNA-positive-stranded, large virus [18]. The RNA contains open-reading frames encoding a large polyprotein needed for viral replication, the spike protein (S), an envelope protein (E), membrane protein (M), nucleocapsid (N), which are the four structural proteins and eight polypeptides [19]. Three vaccine types were developed for SARS [17,20,21]. The first generation was the inactivated SARS-CoV-based vaccine which would elicit viral-neutralizing antibodies. This was developed by treating the SARS-CoV virus using formaldehyde, ultraviolet light, or beta-propiolactone. The whole virus vaccine effectively elicits an immune response in animal models. Still, it cannot be deemed safe for human use as the complete antigenic properties of all structural proteins of the virus are unknown. Extreme caution needs to be used in production since workers will have to handle a high concentration of virus [17,19–22]. The SARS-CoV S protein is a transmembrane glycoprotein with three components: extracellular, transmembrane, and intracellular. The extracellular domain has a receptor-binding domain and attaches to angiotensin-converting enzyme 2 (ACE2), which initiates the infection [23]. Vaccines able to strengthen immune response by triggering a huge antibody production were planned to stop the S protein binding to the host cells and represented the second type of vaccine studied. Many genetically engineered, attenuated, and vaccine vectors have also been considered encoding the virus's S protein [1,17,19]. Analysis of sera from SARS patients revealed five immunodominant sites (IDS) in the S protein, with the fifth being the most immunodominant. IDS peptides could elicit high titers of S protein-specific antibodies, but there was not much evidence to neutralize the antigens. It was unclear whether this would enhance infection or neutralize it [24,25]. The third type of vaccine is a recombinant receptor-binding domain (RBD) antibody that can bind to the RBD of S protein and neutralize the virus. This was successful in mice models [1,17,19].

In a comparative study conducted by See et al., two SARS vaccines were compared (whole killed virus (WKV) and adenovirus vector vaccine (Ad S/N)). It was reported that the WKV vaccine was more effective than the adenovirus vector-based vaccine. After the SARS-CoV challenge, the results showed a reduced viral load in mice's respiratory tract with the WKV vaccine [26]. On the other hand, the intranasal administration of the adenovirus vector vaccine-elicited considerable protection in mice. This study helps understand which vaccine can be pushed to study in a human model [26]. Using a whole killed virus vaccine in ferrets and monkeys in preclinical trials demonstrated an immunopathogenic-type pulmonary disease [27]. Some prior experiences with RSV (respiratory syncytial virus) vaccinated children showed

an increase in severity of naturally occurring RSV disease, even leading to hospitalization and death [27]. Further investigation into these vaccines was shelved due to various reasons.

1.1.2. MERS

The Middle East respiratory syndrome coronavirus (MERS-CoV) affected over 2400 people in 2012. The case fatality rate associated with MERS is 34.5% [28,29]. As in the case of SARS and COVID-19, symptoms included fever, shortness of breath, and in severe cases leading to pneumonia requiring ventilation support [30]. MERS-CoV is a positive-stranded RNA virus of the Coronaviridae family with at least ten open reading frames (ORFs) encoding four structural proteins (spike S, envelope E, membrane M and nucleocapsid N), 16 non-structural proteins, and five accessory proteins. The S and N proteins are of particular interest as these are enabled with eliciting a T-cell response and are highly immunogenic. The S protein induces neutralizing antibodies [31]. In dromedary camels, S-specific antibodies were isolated in affected areas such as Saudi Arabia, Jordan, Qatar, and the United Arab Emirates [32]. MERS vaccines have been extensively researched and have even cleared preclinical trials, although there is no approved vaccine to this day [33,34]. Vaccination may activate B-cells to secrete IgG and secretory IgA antibodies, both of which attach to the virus and mediate mucosal and systemic immune response [32]. Many animal models such as rhesus macaques, marmosets, and transgenic mice have been developed for preclinical studies [32,35].

Six different vaccines are under study for MERS [36]. Recombinant MERS-CoV vaccines induced humoral and T-cell mediated immune response and neutralizing antibodies in mice, but the possibility of virulence recurrence is high. The viral-vector-based vaccines protected transduced mice when challenged with MERS-CoV, and in dromedary camels, the viral lung titers were considerably low. The chances of non-neutralizing immune reaction to epitopes of full-length S protein are possible. Nanoparticle vaccines were effective in mice in the presence of an adjuvant (Matrix M1). DNA vaccines could elicit antigen-specific neutralizing antibodies in mice, non-human primates (NHPs), and camels and be found to protect NHPs when challenged with the virus. DNA prime/protein-boost vaccines could induce strong serum-neutralizing antibodies in mice and NHP models and protected NHPs on the challenge. DNA prime vaccines require an adjuvant like alum. Subunit vaccine induces potent neutralizing antibodies in mice and rabbit models [32,37]. It elicited T-cell responses in mice and protected NHPs on the MERS-CoV challenge. Subunit vaccines require appropriate adjuvant and need to maintain suitable protein conformation [31,32]. One study conducted by Doremalan et al. researched the replication-deficient simian adenovirus vaccine vector (ChAd) encoding a full-length MERS-CoV S protein (ChAdOx1 MERS) vaccine in NHPs (rhesus macaques) [30]. The macaques were administered a single dose of the vaccine and were challenged with the virus but did not develop any disease [35]. A first-in-human phase 1 study has been commenced using the MERS DNA vaccine. This breakthrough is to develop vaccines and help protect the affected region from the disease [38].

1.2. Vaccine candidates for COVID-19

1.2.1. Vaccines in the clinical trial stage

Until the end of 2020, the response to the pandemic has been to implement case identification, isolation, contact tracing, and physical distancing. The UK Imperial College's response team has speculated that once these preventive measures are reversed, there may be a quick rebound of transmission [114]. Additionally, WHO has revealed a warning of multiple outbreaks occurring worldwide simultaneously [115]. Vaccine development is of utmost priority to effectively control the spread of COVID-19 [4]. The adaptive immune responses play a vital role in successful vaccination. With SARS, seroconversion was observed between 4 and 14 days, and neutralizing antibodies were observed almost two years after infection. In SARS-CoV infected patients, a strong

T-cell response leads to higher neutralizing antibodies [24,39]. Most responses were found against the spike protein epitope of the SARS-CoV virus. The genetic similarity of the SARS-CoV-2 to SARS-CoV shows promise in exploring these immune processes for vaccine development. This has sped vaccine development due to existing knowledge [40]. Vaccine approaches include recombinant subunit vaccines, DNA vaccines, and mRNA vaccines [1,41]. One study conducted *in-silico* identified potential vaccine target epitopes, 28 peptides studied with the SARS outbreak, and 48 peptides that had similarities to epitopes previously identified [42]. Another study found that vaccines targeting the S1 subunit of the spike protein may not be as effective as those targeting the S2 subunit [43]. This indirectly relates to the type of immune response they mediate. The S1 subunit induces a B-cell response, and the S2 subunit induces a T-cell response known to have long-lasting antibodies in studies on SARS-CoV [43,44].

It has been reported that 114 vaccine candidate vaccines are in clinical trials against SARS-CoV-2 (29 vaccines in phase 1, 16 vaccines in phase 2, and 37 vaccines at phase 3) [45,46]. However, ten vaccines from China and Russia based on the adenovirus and protein, from France based on mRNA vaccine, from Imperial College London based on a “self-amplifying” RNA vaccine, from New Jersey-based OncoSec Immunotherapies based on a loop of DNA that encodes both IL-12 and the spike protein, Merck company based on the project of Themis and IAVI on a second viral vector vaccine, Maryland-based Altimmune based on Ad5 adenovirus, SK Bioscience, a South Korean vaccine maker based on fragments of the spike protein, Australia's University of Queensland based on combining coronavirus spike proteins with an adjuvant made by CSL as well as Iran's Ministry of Defense based on inactivated coronaviruses are at the early or limited approval, and they have been certified without the results confirmation of Phase 3 trials.

The adenovirus type 5 vector (Ad5-nCoV by CanSino Biological Inc./Beijing Institute of Biotechnology) is a non-replicating viral vector currently entered Phase 2 clinical trials [44]. Safety, immunogenicity, and tolerability of an aerosolized adenovirus type-5 vector-based COVID-19 vaccine (Ad5-nCoV) in adults showed two doses of this vaccine-induced neutralizing antibody responses, similar to one dose of intramuscular injection [47]. Another investigation also showed that the heterologous recombinant adenovirus type 26 (rAd26) vector and a recombinant adenovirus type 5 (rAd5) vector-based COVID-19 vaccine has a good safety profile and stimulated strong cellular and humoral immune responses in participants [48]. The genetically modified vector vaccine is made non-replicative and made to express the spike protein of SARS-CoV-2. Previous experiences with such vaccines have been successful with Ebola [49]. In March, 108 volunteers participated in the first phase of the CanSino Biologics study in China. The second phase of the trial was carried out in Wuhan city with the participation of 508 people. The results of two phases of studies were published recently [44]. According to the report, the investigated vaccine is safe. It induces a significant humoral and cellular immune response in most vaccinated people after receiving a single dose of the vaccine. Another adenovirus vector vaccine is developed by the University of Oxford (ChAdOx1) [50]. Also, a genetically modified non-replicative vaccine is designed to express the S protein of SARS-CoV-2 to elicit immunity. Phase 1 trials have shown to be safe, well-tolerated, and with no major side effects [51]. Immunogenicity and safety of ChAdOx1 MERS vaccine candidate in a trial in the UK in healthy Middle Eastern adults (MERS002) support selecting the ChAdOx1 MERS vaccine for phase 2 clinical evaluation [52].

The second vaccine entered into a Phase 1 trial is the DNA plasmid vaccine administered through electroporation (INO-4800). It was immunogenic in 100% of the vaccinated participants and induced good tolerability and safety by stimulating cellular or humoral immune responses. [53,54]. Immunogenicity and safety of INO-4800 DNA vaccine against SARS-CoV-2 were shown in Phase 2 clinical trial in adults with a high risk of viral exposure [55].

Viruses used as vectors include the vaccinia virus, measles virus, and

adenovirus (that causes the common cold) [56].

Inovio Pharmaceuticals, in association with Beijing Advanced Biotechnology, developed a vaccine as previously for HIV, Nipah, Hepatitis B, Zika, and cancer therapy [53]. The INO-4800 vaccine elicits a T-cell response through the DNA plasmids. This platform's main advantage is that it activates the immune response and adds therapeutic antibodies intradermally [41,54,55,57].

Two inactivated viral vaccines have been developed by the Beijing Institute of Biological Products/Wuhan Institute of Biological Products and Sinovac. These vaccines are currently in phase 3 trials approved in China and have emergency use in other countries [58]. In a study conducted by Gao et al., the Sinovac developed PiCoVacc, a purified inactivated CN2 strain of virus, was studied in mice models, and the result was very promising [59]. Upon administration of PiCoVacc mixed with alum adjuvant and serological testing of mice revealed similarity to blood recovered from patients who recovered from COVID-19. Similar results were observed upon administering three vaccine doses to rhesus macaques [59].

An mRNA vaccine in phase 3 trials that were developed by Moderna, Inc. in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), the LNP-encapsulated mRNA (mRNA-1273) encodes the viral spike (S) protein. A breakthrough with this vaccine is that it was developed *in-silico* and did not require cell culture, and this will help immensely with rapid development and manufacturing. An mRNA vaccine's main advantage is that it lacks genome integration with the host [41]. Another candidate mRNA vaccine developed by BioNTech in collaboration with Fosun Pharma and Pfizer has been approved and granted by Food and Drug Administration the vaccine and World Health Organization in an Emergency Use Listing [60,61].

Advances in technology and a solidarity approach to research and testing are paving a new path in vaccine development in these times. Every day new vaccine models are being tested and approved for a human trial, and the turnaround time for preclinical trials is shortened significantly due to sharing more information. There is no doubt that more candidate vaccines will be available for clinical trials soon.

1.3. Vaccines in the preclinical stage

As of January 2022, the global vaccine R&D against COVID-19 includes about 114 clinical trial evaluations in humans and 75 in the preclinical stage in animals, and 18 approved for emergency use. Many novel technology platforms have been evaluated as part of vaccine development. Platforms such as DNA and RNA, virus-like particles, viral vectors, recombinant protein, live attenuated virus, and inactivated viruses have been studied. Some of these are not typical platforms used in active vaccinations, but oncology breakthroughs have led researchers to pursue these new platforms. The advantages include a quick development time and manufacturing [10].

1.4. Whole virus vaccine

Usually, an inactivated whole virus vaccine is the classic approach for viral vaccinations. A whole virus vaccine's features are that they have inherent immunogenicity and can elicit Toll-like receptors (TLRs). Still, the major disadvantage is that they can sometimes increase disease severity, requiring stringent safety tests [62]. There are currently four live attenuated and sixteen three inactivated candidate SARS-CoV-2 vaccines in clinical trials on humans [63,64]. The most important benefits of the live-attenuated SARS-CoV-2 vaccine are stimulating and targeting potent cellular and mucosal immunity, which is critical for viral [65]. The disadvantage of SARS-CoV-2 is the potential excretion of live-attenuated SARS-CoV-2 vaccines in the feces of vaccinated people and possible transmission of SARS-CoV-2 to unvaccinated individuals [66].

Moreover, the risk of recombination between circulating wild-type virus and the vaccine strain may be increased through the

administration of the live-attenuated SARS-CoV-2 vaccine and induce the generating of new variants of SARS-CoV-2. However, the formulation and production of a live attenuated SARS-CoV-2 vaccine requires rigorous quality control and is labor-intensive [67]. Inactivated SARS-CoV-2 virus technology has been approved through the Chinese companies Sinopharm-Beijing, Sinopharm-Wuhan, and Sinovac [68]. The phase 3 trial started in the United Arab Emirates, Morocco, and Peru. Bahrain and U.A.E. approved Sinopharm's vaccine to use on government officials and health care workers. It was 79.34% effective [69]. Johnson & Johnson is currently designed as an adenovirus vector-based whole viral vaccine similar to their Ebola vaccine with a key part of the SARS-CoV-2 virus that induces an immune response. [70,71]. A live influenza vaccine that expresses SARS-CoV-2 protein is under development at the University of Hong Kong. Codagenix, in collaboration with the Serum Institute of India, has developed a live attenuated vaccine in preclinical trials. Codagenix optimizes the viral genes by using algorithms that multiply slowly in the host [72]. Also in preclinical trials is the German Centre for Infection Research's live attenuated measles virus with S and N targets, which is also a candidate for Zika [73]. The Novartis Company also will manufacture a vaccine based on an adeno-associated virus (AAV) vector technology that delivers coronavirus gene fragments into cells [68,74]. The Chinese company CanSino Biologics also developed a vaccine according to an adenovirus with promising results from phase 3 trials that demonstrated the vaccine stimulated a potent immune response [75,76]. However, CanSino started phase 3 trials in several countries such as Pakistan, Russia, Mexico, Chile, and Saudi Arabia. China also approved the CanSino vaccine for general use. The University of Queensland has designed the synthesizing of viral surface proteins with funding from the Coalition for Epidemic Preparedness Innovations (CEPI) that effectively activates the host immune responses [77].

1.5. Subunit vaccines/protein-based vaccines

Subunit vaccines and protein-based vaccines are relatively safe and easy to produce that well-tolerated regarding to whole virus vaccines. The low immunogenicity of this kind of vaccine is their limitation. Therefore, adjuvants are usually used to improve their immunogenicity. Subunit vaccine approaches include using the S-spike protein of SARS-CoV-2 and eliciting an immune response against it [78]. This prevents the virus from binding with the host ACE-2 receptors [39]. There exists a risk of higher infectivity and eosinophil filtrations. The University of Queensland has begun synthesizing viral surface proteins with funding from CEPI. Novavax has produced a recombinant S-protein based on virus-like nanoparticles, and Clover Biopharmaceuticals has progressed with a trimerized S protein subunit vaccine with their patented Trimer-Tag® technology. In collaboration with the University of Texas and New York Blood Centre, Texas Children's Hospital Centre for Vaccine Development has developed a receptor-binding domain (RBD) of S protein-only vaccine [79]. Also, adjuvant-like alum has elicited high levels of immunity in test models. The advantage of the RBD-based vaccine is that it displays very low chances of host immune potency. Immunization with adjuvanted S-Trimer of COVID-19 with an oil-in-water emulsion of AS03 or TLR9 agonist (CpG 1018) plus alum adjuvants stimulated high-level of Th1-biased cellular immune responses and neutralizing antibodies in animal models [80]. Moreover, another study reported strong neutralization antibodies stimulated by a recombinant based protein of trimeric spike of COVID-19 adjuvanted by PIKA [81]. Immunogenicity and safety of recombinant S-Trimer of COVID-19 also reported in healthy adults through the potent humoral responses and neutralizing antibodies [82].

Moreover, a Russian biological research center named Vector Institute designed a small portion of viral proteins called EpiVacCorona that is in the phase 3 trial and showed that it is a safe vaccine with low reactogenicity [83]. Many other privately helped firms have developed subunit vaccines using various vectors, which are in preclinical trials. These companies include BioVaxys Technology; Applied Biotechnology

Institute; City College of New York and TechnoVax; Doherty Institute and Monash University; Dyadic and Sorrento; EpiVax; Eyegene and Pharmcadd; Generex; GeoVax; Heat Biologics; iBio; Iconovo and ISR; ImmunoPrecise Antibodies; IMV; Inserm, Vaccine Research Institute and Université Paris-Saclay; Instituto Buntantan; Intravacc; IrsiCaixa; Izmir Biomedicine and Genome Center; MIGAL Galilee Research Institute; Nanografi Nano Technology, Middle East Technical University, and Ankara University; Navarrabiomed; Neo7Logix; NidoVax; Novavax; OncoGen; Oragenics; Osaka University, BIKEN, and National Institutes of Biomedical Innovation, Japan; Osivax; PDS Biotechnology; Quadram Institute; Reliance Life Sciences; ReVacc Biotech; Soligenix; Uvax; University of Pittsburgh; University of San Martin and CONICET, Argentina; University of Sao Paulo; University of Virginia; Vaxxas, University of Queensland and Griffith University; Voltron Therapeutics; Walter Reed Army Institute of Research. A total of 46 subunit vaccines are in pre-clinical trials [41,73].

1.6. DNA and mRNA vaccines

The idea of immunizing with DNA was conceptualized with good results in 1993 in mice models [84]. Mice were vaccinated with DNA against influenza, showing considerable immunity [85]. This concept is not proven yet in humans and may need additional research before approval [86]. DNA vaccines will not be the quickest route for the COVID-19 situation. Inovio has successfully entered phase 1 trials with their DNA vaccine. Karolinska Institute / Cobra Biologics has developed a DNA vaccine with electroporation that is in phase 1 trials [87,88]. Osaka University with Takar Bio has a DNA plasmid vaccine in phase 2/3 trials [7]. Immunomic Therapeutics, Inc./EpiVax, Inc./PharmaJet, Inc. have also developed a needle-free delivery vaccine with DNA plasmid in phase 1 trials [88]. Other organizations such as Zydus Cadila (phase 3), BioNet Asia (phase 1), and the University of Waterloo have DNA vaccines in clinical studies [73,89]. In partnership with Translate Bio, Sanofi is developing an mRNA vaccine that produces a potent antibody response in monkeys and mice, which they followed up Phase 1/2 trial in March 2021 [79,90].

1.7. Virus-like particle vaccine

Virus-like particle (VLP) vaccines are a subunit vaccine class that mimics an actual virus particle structure without virulence. They are safer than whole inactivated vaccines or attenuated vaccines as they cannot genetically reverse to being pathogenic. They elicit a stronger immune response than single protein-based vaccines [91]. Moreover, they are administered through the mucosal to target the pulmonary system [92]. VLP vaccines for SARS-CoV were successful in mice models. Novavax had a nanoparticle VLP vaccine under development for MERS-CoV, which was successful in mice and cattle [93]. Medicago Inc. has developed a plant-based VLP vaccine which is in Phase 2/3 trial [94]. Imophoron Ltd., with Bristol University's Max Planck Centre and Doherty institute, is currently in preclinical trials with their candidate VLP vaccines [87,95,96].

1.8. Non-specific vaccines

1.8.1. BCG vaccine

The Bacillus Calmette–Guérin (BCG) is an attenuated *Mycobacterium bovis* vaccine used to protect from tuberculosis. BCG use is highly prevalent as a routine vaccination for infants and neonates in many countries. Its main utility is preventing tuberculosis meningitis and disseminated tuberculosis [97]. Although not extensively studied in humans, the BCG vaccine has shown some heterologous beneficial properties against non-related infections. In a study (randomized placebo-controlled human challenge), BCG vaccination-induced genome-wide epigenetic reprogramming of monocytes when challenged with an attenuated yellow fever virus vaccine strain [98]. This

shows that the BCG vaccine successfully induces immunity, *in vivo*, against other non-related viral infections [99]. This occurs due to monocytes' epigenetic reprogramming, increasing cytokine production when exposed to a non-related pathogen, for up to 3 months after vaccination. This phenomenon is termed 'trained immunity' (mediated by Interleukin-1 β). Another study explored the extent of the trained immunity one year after vaccination by measuring the heterologous T helper 1 (Th1) and Th17 immune cells. The study proved that even 1 year after vaccination with BCG, sustained innate immunity and a heterologous Th1/Th17 responses were present against non-specific infections [98].

In the current COVID-19 scenario, a non-peer-reviewed study was published that studied the patterns of BCG vaccination country-wise and its impact on COVID-19 [100]. The national policy on BCG vaccination varies widely by country. In general, it was found that countries without universal BCG vaccination programs were more severely affected. This includes countries like Italy, the Netherlands, USA. The pandemic appeared less severe in countries with a long-standing BCG vaccination program policy with a markedly lower fatality rate [101]. In some countries like Iran, which commenced the BCG program much more recently, the fatality rate was high since the elderly population was never exposed to the BCG vaccine [102]. Although a little early to say, preliminary data suggests that the number of reported COVID-19 positive cases in countries with a BCG program was lower in number [102,103]. However, this association between the BCG vaccine and lower COVID-19 cases could not be interpreted as a cause-effect relationship since it is only a statistical association that should be confirmed by more interventional studies. Despite this fact, the BCG vaccine could be a new promising tool in the fight against SARS-Cov-2 [104]. [68].

1.9. Vaccine development in pandemic paradigm

Other population health problems and pandemics in the past have proven to be a learning experience in the field of vaccine development. Openly shared research, innovation, and global coordination have been identified as key contributors to vaccine development. Due to many regulatory processes for licensing and post-marketing surveillance, the influenza vaccine was available almost after a 6-month delay, by which time the pandemic had peaked. Another challenge to address was the manufacturing capacity for mass production of vaccines. Major learning was vaccine timing. Like with the H1N1 2009 pandemic, many countries received vaccine lots only after some countries had either begun or completed their vaccination programs [105,106]. As a result of these, today, many guidelines exist to manage vaccine preparedness, surveillance, and pre-qualification [105,106].

CEPI supports vaccines' development for five epidemic diseases defined by WHO [107]. Their goal is to create reserves of investigational vaccines that have completed Phase 2a trials, begin clinical trials during the next epidemic, and speed up vaccine production. CEPI has developed a technology platform for novel virus pandemics such as COVID-19, using which viral sequencing to enter clinical trials can be completed in 6 weeks [107]. The most promising vaccines in terms of speed are DNA and RNA vaccines, as they do not require cultures or fermentation and can be synthesized quickly. The next probability would be recombinant subunit vaccines. With the advancement in technology, the use of next-generation sequencing and reverse genetics can cut development time.

One of the major challenges with SARS-CoV-2, although the spike protein offers the best immunogenic response route, optimizing antigen design is needed. Debate is still ongoing if the vaccine should target the entire spike protein or only the receptor-binding domain. Experience with SARS and MERS raises concerns about exacerbating the infection due to antibody-dependent enhancement. The question of the validity of protection also still lingers. Assessing the number of doses is a time-consuming process as it is key first to get results on how long the immunity lasts after vaccination [108].

Developing a vaccine in a pandemic paradigm incurs extra costs and risks. Unlike traditional development, pandemic vaccine development cannot happen sequentially. Multiple steps are to be carried out simultaneously without awaiting the results of the previous step. The chance of failure with high investment is a heavy possibility. CEPI commenced developing vaccines with partners as soon as the genetic sequence of SARS-CoV-2 was made available. Moderna entered their candidate vaccine into Phase 1 trials in less than ten weeks. Phase 2 trials need to be conducted almost simultaneously with bulk vaccine production, and the trials themselves need to be performed simultaneously for multiple candidates [109]. The demand for vaccines increased worldwide and required a fair allocation system globally [108].

1.10. Approved and limited vaccines

Vaccines approved for full use are mRNA-based and non-mRNA-based vaccines produced by different countries. These include the German company BioNTech in collaboration with New York-based Pfizer and the Boston-based Company Moderna with 95% and 94.5% effective immune responses [60,110]. The BioNTech researchers manufactured the vaccine based on genetic instructions for building coronavirus spike protein. After injection, the vaccine induces spike proteins' production in the cells, which stimulates a potent response from the immune system to induce antibodies against SARS-CoV-2. Phase 2/3 trial vaccine has been performed with 30,000 volunteers in the United States and other countries like Brazil, Germany, and Argentina [79]. Pfizer and BioNTech also released the FDA independent analysis of the clinical trials. They reported 95% of efficacy for their vaccine. It has been revealed that Latino, white, and Black volunteers have little difference in their protection. Besides, people with diabetes or obesity showed the same protection level—the same efficacy rate of under 65 has been reported in older adults. However, without documented serious side effects, the BioNTech vaccine-induced fever, muscle aches, and short-lived fatigue [111]. Similar to BioNTech and Pfizer, Moderna produces its mRNA vaccine for coronavirus. Recently, this company has tested an mRNA vaccine that protects monkeys from the coronavirus. After promising results, phase 3 testing on 30,000 volunteers started on 27 July 2020. The scientists proposed 94.1% of efficacy for this vaccine, and it is not reported how long this efficacy will last. Moderna has announced that a strong immune defense against the coronavirus has been detected after three months of vaccination.

On the other hand, a vaccine has been canceled from the University of Queensland in Australia after entering a clinical trial on 10 December 2020 because of worrying symptoms in volunteers. This vaccine was based on coronavirus spike proteins combined with GlaxoSmithKline's proprietary adjuvants made by CSL. The animal studies on hamsters offered great responses from the coronavirus at first for this vaccine (University of Queensland 2020 Significant step' in COVID-19 vaccine quest. uq.edu.au 21 February). However, before the late-stage trials of this vaccine, an unwelcome discovery has occurred, and some volunteers were shown positive tests for HIV. Nevertheless, they were not contaminated with that HIV. According to these reports, the trouble appears to be because unfolded spike proteins cannot work against real viruses' antibodies. So the researchers create a little clamp at one end of the protein to preserve the molecule's proper shape. Unfortunately, the designed clamp resembles an HIV protein, which induces the immune system to produce HIV-like antibodies [112].

1.11. Limitations

Vaccines for diseases like COVID-19 need to be developed from scratch and the time required for such development is immense. This means that a safe and effective vaccine is developed when the public health threat has long been overcome, ending any further development in the space. Vaccine development goes through design, production, purification, animal testing to check for safety, and four phases of

human testing. Phase 1 of testing is done for safety, and phases 2 and 3 are for efficacy. Developing a vaccine is taking a risk and counting on the infection being still circulating when they reach phase 2 and 3 trials [10,113–115]. There is still an enhanced safety concern in vaccine science, complicated manufacturing processes, and assay requirements. New rules have to be made in manufacturing and regulatory processes to produce a vaccine at the time of a pandemic quickly. The challenge remains in quickly organizing efficacy studies and finding the right animal models extremely valuable in vaccine development. One work-around is improving traditional development and making way for newer vaccine technologies, which have previous human study experience. It is also vital to assess if the developer can scale up the development model to produce nearly 10 million vaccine doses, keeping in line with GMP. Any manufacturer with recent production experience will be in a favorable position [92].

Regulatory challenges to prove the safety of the vaccine become an issue. It is important to prove that the vaccine will not elicit the same detrimental immune responses a virus-like SARS-CoV-2 elicits in the body. This affects the type of immunogens and, ultimately, the type of vaccine. Commercial manufacturing is different from development manufacturing and requires to be validated. The question remains whether the same regulatory standards hold well across countries or whether the safety and regulations must be revisited. Cell banks and other products need to be accepted globally, across borders, so do the commercial and political barriers [92]. Lastly, for the entire world to get a fair share of the vaccine, a few things need to be addressed, such as vaccine ownership, production funding at a large scale, pricing, and supply, coordinated administration to achieve the best outcome during a pandemic [92,108].

2. Conclusion

Today a vaccine to address the COVID-19 pandemic situation globally is needed. Several candidate vaccines are already in various phases of clinical trials. Although vaccine development for this pandemic has happened incredibly fast, it is crucial to thoroughly check safety as no licensed coronavirus is available to date after two previous epidemics. The DNA and RNA vaccines show the most promise in terms of speed of development and safety. Initially, priority for vaccines will be given to healthcare workers and those at risk of severe disease and death. It is important to ensure that high-income companies do not monopolize vaccine supply, which was the case during the H1N1 pandemic. Regulatory frameworks need to consider an equal supply of already scarce vaccines across all countries with different economic statuses.

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